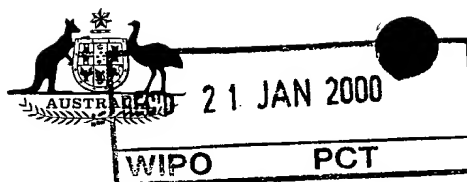


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I, LEANNE MYNOTT, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PQ 3568 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. filed on 21 October 1999.

WITNESS my hand this  
Sixth day of December 1999

*L. Mynt*

LEANNE MYNOTT  
TEAM LEADER EXAMINATION  
SUPPORT AND SALES



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Fujisawa Pharmaceutical Co., Ltd.

**A U S T R A L I A**  
**Patents Act 1990**

**PROVISIONAL SPECIFICATION**  
for the invention entitled:

"Piperazine Derivatives"

The invention is described in the following statement:

## D E S C R I P T I O N

## PIPERAZINE DERIVATIVES

## 5 TECHNICAL FIELD

The present invention relates to new piperazine derivatives and a salt thereof.

More particularly, it relates to new piperazine derivatives and a salt thereof which have pharmacological  
10 activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament.

15 Accordingly, one object of the present invention is to provide new and useful piperazine derivatives and a salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the  
20 like.

Another object of the present invention is to provide a process for the preparation of said piperazine derivatives and a salt thereof.

A further object of the present invention is to provide  
25 a pharmaceutical composition comprising, as an active ingredient, said piperazine derivatives and a pharmaceutically acceptable salt thereof.

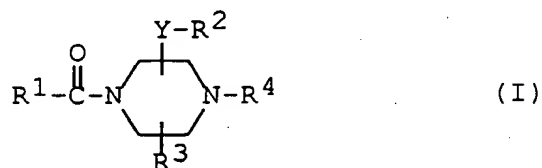
Still further object of the present invention is to provide a use of said piperazine derivatives or a  
30 pharmaceutically acceptable salt thereof as Tachykinin antagonist, especially Substance P antagonist, Neurokinin A antagonist or Neurokinin B antagonist, useful for treating or preventing Tachykinin-mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis,  
35 cough, expectoration, and the like; ophthalmic diseases such

as conjunctivitis, vernal conjunctivitis, and the like;  
 cutaneous diseases such as contact dermatitis, atopic  
 dermatitis, urticaria, and other eczematoid dermatitis, and  
 the like; inflammatory diseases such as rheumatoid arthritis,  
 5 osteoarthritis, and the like; pains or aches (e.g., migraine,  
 headache, toothache, cancerous pain, back pain, etc.); and  
 the like in human being or animals.

Some piperazine derivatives having pharmaceutical  
 10 activities such as Tachykinin antagonism have been known as  
 described in EP 0655442 A1 and WO 97/22597 A1.

#### DISCLOSURE OF INVENTION

The object compound of the present invention can be  
 15 represented by the following general formula (I):



20 wherein

Y is bond or lower alkylene,

R<sup>1</sup> is aryl which may be substituted with suitable  
 substituent(s),

25 R<sup>2</sup> is aryl or indolyl, each of which may be substituted with  
 suitable substituent(s),

R<sup>3</sup> is hydrogen or lower alkyl,

R<sup>4</sup> is (3-pyridyl)methyl;

(3-pyridyl)ethyl;

30 3-(3-pyridyl)propyl;

3-(3-pyridyl)propenyl;

3-(3-pyridyl)propynyl;

pyrazolylmethyl which may be substituted with  
 hydroxy(lower)alkyl;

35 pyrazolyl(lower)alkyl which is substituted with lower

alkyl, (lower)alkoxy(lower)alkylmorpholinyl(lower)alkyl  
or (lower)alkoxy(lower)alkylmorpholinylcarbonyl(lower)-  
alkyl;

piperidylmethyl;

piperidyl(lower)alkyl which is substituted with lower  
alkyl or (lower)alkoxy(lower)alkyl;

(2,6-dimethylmorpholino)(lower)alkyl;

(3,3-dimethylmorpholino)(lower)alkyl;

(cis-3,5-dimethylmorpholino)(lower)alkyl;

((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl;

(2-methoxymethylmorpholino)(lower)alkyl;

(3-methoxymethylmorpholino)(lower)alkyl;

(2-methoxymethyl-5-methylmorpholino)(lower)alkyl;

(2-methoxymethyl-5,5-dimethylmorpholino)(lower)alkyl;

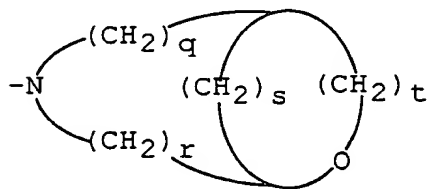
(3,5-dimethoxymethylmorpholino)(lower)alkyl;

(2,3-dimethoxymethylmorpholino)(lower)alkyl;

(2-methoxymethylmorpholino)(lower)alkenyl;

(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)(lower)alkyl;

or lower alkyl which is substituted with a saturated  
heterocyclic group of the formula:



(wherein

r, s and t are each integer  
of 1 to 2, and

q is integer of 0 to 2)

which may be substituted with one or two lower alkyl.

It is to be noted that the object compound (I) may  
include one or more stereoisomers due to asymmetric carbon  
atom(s) and double bond, and all of such isomers and a  
mixture thereof are included within the scope of the present  
invention.

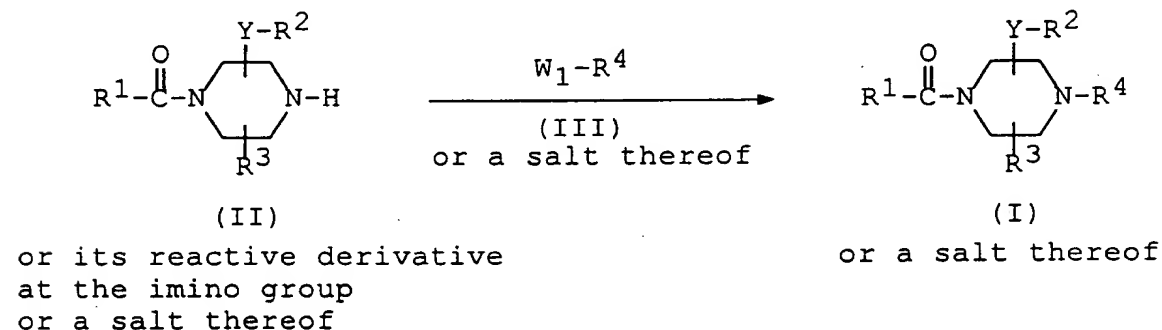
It is further to be noted that isomerization or  
rearrangement of the object compound (I) may occur due to the

effect of the light, acid, base or the like, and the compound obtained as the result of said isomerization or rearrangement is also included within the scope of the present invention.

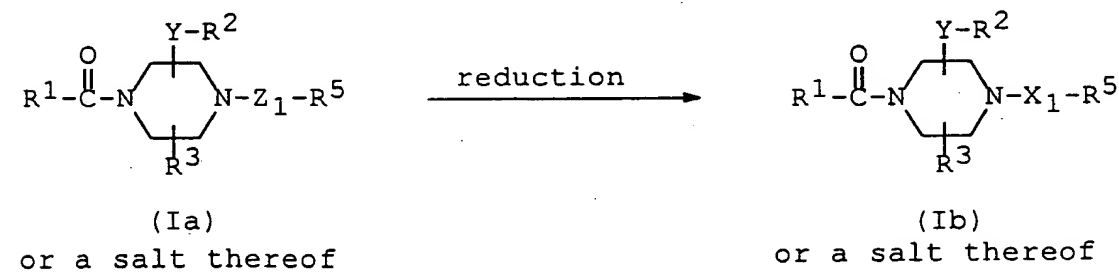
It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

According to the present invention, the object compound (I) or a salt thereof can be prepared by processes which are illustrated in the following schemes.

#### Process 1



#### Process 2



wherein

Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each as defined above,

X<sub>1</sub> is lower alkylene,

Z<sub>1</sub> is lower alkynylene,

R<sup>5</sup> is 3-pyridyl, and

$W_1$  is a leaving group.

As to the starting compounds (II) and (III), some of them are novel and can be prepared by the procedures described in the Preparations and Examples mentioned later or similar manners thereto.

Suitable salts of the starting and object compounds are conventional non-toxic and pharmaceutically acceptable salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, fumarate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.), or a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), or a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise indicated.

Suitable "lower alkylene" may include straight or branched one having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, propylene, tetramethylene, methylmethylene, methyltrimethylene, hexamethylene, and the



like, in which the preferred one is methylene, ethylene, trimethylene or methylenemethylene.

Suitable "lower alkynylene" may include one having 2 to 6 carbon atoms, such as ethynylene, propynylene, butynylene, and the like, in which the preferred one is propynylene or butynylene.

Suitable "halogen" and "halogen" moiety in the terms "mono(or di or tri)halo(lower)alkyl", "mono(or di or tri)halo(C<sub>1</sub>-C<sub>4</sub>)alkyl", etc. may include fluorine, chlorine, bromine and iodine.

Suitable "lower alkyl" and "lower alkyl" moiety in the terms "hydroxy(lower)alkyl", "pyrazolyl(lower)alkyl", etc. may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl and the like, in which the preferred one is C<sub>1</sub>-C<sub>4</sub> alkyl and the most preferred one is methyl or isopropyl.

Suitable "lower alkenyl" moiety in the term "(2-methoxymethylmorpholino)(lower)alkenyl" may include vinyl, 1-(or 2-)propenyl, 1-(or 2- or 3-)butenyl, 1-(or 2- or 3- or 4-)pentenyl, 1-(or 2- or 3- or 4- or 5-)hexenyl, methylvinyl ethylvinyl, 1-(or 2- or 3-)methyl-1-(or 2-)propenyl, 1-(or 2- or 3-)ethyl-1-(or 2-)propenyl, 1-(or 2- or 3- or 4-)methyl-1-(or 2- or 3-)butenyl, and the like, in which more preferable example may be C<sub>2</sub>-C<sub>4</sub> alkenyl.

Suitable "aryl" may include phenyl, naphthyl, and the like, in which the preferred one is C<sub>6</sub>-C<sub>10</sub> aryl and the most preferred one is phenyl or naphthyl.

Suitable "lower alkoxy" and "lower alkoxy" moiety in the terms "(lower)alkoxy(lower)alkylmorpholinyl(lower)alkyl", "(lower)alkoxy(lower)alkylmorpholinylcarbonyl(lower)alkyl", etc. may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like, in which the preferred one is C<sub>1</sub>-C<sub>4</sub> alkoxy and

the most preferred one is methoxy.

Suitable "substituent" in the terms "aryl which may be substituted with suitable substituent(s)" for R<sup>1</sup> and "aryl or indolyl, each of which may be substituted with suitable substituent(s)" for R<sup>2</sup> may include lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, tert-pentyl, hexyl, etc.), lower alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, propylenedioxy, etc.), lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, tert-butoxy, pentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy, etc.), lower alkoxy(lower)alkoxy(lower)alkoxy (e.g., (2-methoxyethoxy)-methoxy, etc.), mono(or di or tri)halo(lower)alkyl (e.g., fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 1 or 2-fluoroethyl, 1 or 2-bromoethyl, 1 or 2-chloroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, etc.), halogen (e.g., chlorine, bromine, fluorine and iodine), hydroxy, hydroxy(lower)alkyl (e.g., hydroxymethyl, hydroxyethyl, 1-hydroxy-1-methylethyl, etc.), cyano, lower alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, etc.), lower alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, etc.), di(lower alkyl)aminosulfonyl (e.g., dimethylaminosulfonyl, diethylaminosulfonyl, etc.), pyrrolidinyl (e.g., 2-pyrrolidinyl, 3-pyrrolidinyl, pyrrolidino, etc.), morpholinyl (e.g., 2-morpholinyl, 3-morpholinyl, morpholino which may be substituted with lower alkyl as mentioned above or lower alkoxy(lower)alkyl (e.g., methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 1-ethoxyethyl, 2-ethoxyethyl, etc.), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, etc.), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl, etc.), and the like.

Suitable "leaving group" may include lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, etc.), aryloxy (e.g., phenoxy, naphthoxy, etc.), an acid residue or the like.

5        Suitable "acid residue" may be halogen (e.g., chlorine, bromine, iodine, etc.), sulfonyloxy (e.g., methanesulfonyloxy, phenylsulfonyloxy, mesitylenesulfonyloxy, toluenesulfonyloxy, etc.) or the like.

10       Preferred embodiments of the object compound (I) are as follows:

Y is lower alkylene (more preferably C<sub>1</sub>-C<sub>4</sub> alkylene, most preferably methylene);

15       R<sup>1</sup> is aryl (more preferably C<sub>6</sub>-C<sub>10</sub> aryl, most preferably phenyl) which may be substituted with 1 to 3 (more preferably 1 or 2, most preferably 2) substituent(s) [more preferably substituent selected from the group consisting of lower alkoxy (more preferably C<sub>1</sub>-C<sub>4</sub> alkoxy, most preferably methoxy), mono(or di or tri)-

20       halo(lower)alkyl (more preferably trihalo(lower)alkyl, most preferably trifluoromethyl), lower alkylthio (more preferably C<sub>1</sub>-C<sub>4</sub> alkylthio, most preferably methylthio), lower alkylsulfonyl (more preferably C<sub>1</sub>-C<sub>4</sub>

25       alkylsulfonyl, most preferably methylsulfonyl), di(lower alkyl)aminosulfonyl (more preferably di(C<sub>1</sub>-C<sub>4</sub> alkyl)aminosulfonyl, most preferably dimethylaminosulfonyl), pyrrolyl (more preferably 1-pyrrolyl) and pyridyl (more preferably 4-pyridyl)];

30       R<sup>2</sup> is aryl (more preferably C<sub>6</sub>-C<sub>10</sub> aryl, most preferably phenyl or naphthyl) or indolyl, each of which may be substituted with 1 to 3 (more preferably 1 or 2) substituent(s) [more preferably substituent selected from the group consisting of lower alkyl (more

35       preferably C<sub>1</sub>-C<sub>4</sub> alkyl, most preferably methyl or

isopropyl), mono(or di or tri)halo(lower)alkyl (more preferably mono(or di or tri)halo(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably difluoromethyl or trifluoromethyl), halogen (more preferably chlorine or fluoride), lower

5 alkylenedioxy (more preferably C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, most preferably methylenedioxy or ethylenedioxy), lower alkoxy (more preferably C<sub>1</sub>-C<sub>4</sub> alkoxy, most preferably methoxy), lower alkoxy(lower)alkoxy(lower)alkoxy (more preferably C<sub>1</sub>-C<sub>4</sub> alkoxy(C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)alkoxy, most

10 preferably (2-methoxyethoxy)methoxy), hydroxy, hydroxy(lower)alkyl (more preferably hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably hydroxymethyl or 1-hydroxy-1-methylethyl), cyano, pyrrolidinyl (more preferably pyrrolidino) and morpholinyl (more preferably

15 morpholino) which may be substituted with lower alkoxy(lower)alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkoxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably methoxymethyl) or lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl, most preferably methyl)];

R<sup>3</sup> is hydrogen; and

20 R<sup>4</sup> is (3-pyridyl)methyl;  
 (3-pyridyl)ethyl (more preferably 2-(3-pyridyl)ethyl);  
 3-(3-pyridyl)propyl;  
 3-(3-pyridyl)propenyl (more preferably 3-(3-pyridyl)-2-propenyl);

25 3-(3-pyridyl)propynyl (more preferably 3-(3-pyridyl)-2-propynyl);  
 pyrazolylmethyl (more preferably (4-pyrazolyl)methyl or (5-pyrazolyl)methyl) which may be substituted with hydroxy(lower)alkyl (more preferably hydroxy(C<sub>1</sub>-C<sub>4</sub>)-

30 alkyl, most preferably 2-hydroxyethyl);  
 pyrazolyl(lower)alkyl (more preferably pyrazolyl-(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably (4-pyrazolyl)methyl, (5-pyrazolyl)methyl or 3-(4-pyrazolyl)propyl) which is substituted with lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub>

35 alkyl, most preferably methyl), (lower)alkoxy(lower)-

alkylmorpholinyl(lower)alkyl (more preferably (C<sub>1</sub>-C<sub>4</sub>)-  
 alkoxy(C<sub>1</sub>-C<sub>4</sub>)alkylmorpholinyl(C<sub>1</sub>-C<sub>4</sub>)alkyl, most  
 preferably 2-(2-methoxymethylmorpholino)ethyl) or  
 (lower)alkoxy(lower)alkylmorpholinylcarbonyl(lower)alkyl  
 5 (more preferably (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)-  
 alkylmorpholinylcarbonyl(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably  
 (2-methoxymethylmorpholino)carbonylmethyl);  
 piperidylmethyl (more preferably (4-piperidyl)methyl);  
 piperidyl(lower)alkyl (more preferably piperidyl(C<sub>1</sub>-C<sub>4</sub>)-  
 10 alkyl, most preferably piperidinomethyl or  
 (4-piperidyl)methyl) which is substituted with lower  
 alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl, most preferably  
 methyl) or (lower)alkoxy(lower)alkyl (more preferably  
 (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably  
 15 ethoxymethyl);  
 (2,6-dimethylmorpholino)(lower)alkyl (more preferably  
 (2,6-dimethylmorpholino)(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably  
 2-(2,6-dimethylmorpholino)ethyl);  
 (3,3-dimethylmorpholino)(lower)alkyl (more preferably  
 20 (3,3-dimethylmorpholino)(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably  
 2-(3,3-dimethylmorpholino)ethyl);  
 (cis-3,5-dimethylmorpholino)(lower)alkyl (more  
 preferably (cis-3,5-dimethylmorpholino)(C<sub>1</sub>-C<sub>4</sub>)alkyl,  
 most preferably 2-(cis-3,5-dimethylmorpholino)ethyl);  
 25 ((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl (more  
 preferably ((3S,5S)-3,5-dimethylmorpholino)(C<sub>1</sub>-C<sub>4</sub>)alkyl,  
 most preferably 2-((3S,5S)-3,5-dimethylmorpholino)-  
 ethyl);  
 (2-methoxymethylmorpholino)(lower)alkyl (more preferably  
 30 (2-methoxymethylmorpholino)(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably  
 3-(2-methoxymethylmorpholino)propyl or  
 2-(2-methoxymethylmorpholino)ethyl);  
 (3-methoxymethylmorpholino)(lower)alkyl (more preferably  
 (3-methoxymethylmorpholino)(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably  
 35 2-(3-methoxymethylmorpholino)ethyl);

(2-methoxymethyl-5-methylmorpholino) (lower) alkyl (more preferably (2-methoxymethyl-5-methylmorpholino)-(C<sub>1</sub>-C<sub>4</sub>) alkyl, most preferably 2-(2-methoxymethyl-5-methylmorpholino) ethyl);

(2-methoxymethyl-5,5-dimethylmorpholino) (lower) alkyl (more preferably (2-methoxymethyl-5,5-dimethylmorpholino) (C<sub>1</sub>-C<sub>4</sub>) alkyl, most preferably 2-(2-methoxymethyl-5,5-dimethylmorpholino) ethyl);

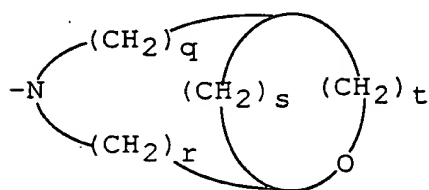
(3,5-dimethoxymethylmorpholino) (lower) alkyl (more preferably (3,5-dimethoxymethylmorpholino) (C<sub>1</sub>-C<sub>4</sub>) alkyl, most preferably 2-(3,5-dimethoxymethylmorpholino) ethyl);

(2,3-dimethoxymethylmorpholino) (lower) alkyl (more preferably (2,3-dimethoxymethylmorpholino) (C<sub>1</sub>-C<sub>4</sub>) alkyl, most preferably 2-(2,3-dimethoxymethylmorpholino) ethyl);

(2-methoxymethylmorpholino) (lower) alkenyl (more preferably (2-methoxymethylmorpholino) (C<sub>2</sub>-C<sub>4</sub>) alkenyl, most preferably 4-(2-methoxymethylmorpholino)-2-butenyl);

(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl) (lower) alkyl (more preferably (5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl) (C<sub>1</sub>-C<sub>4</sub>) alkyl, most preferably 2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl) ethyl); or

lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl, most preferably ethyl) which is substituted with a saturated heterocyclic group of the formula:



(wherein

r, s and t are each integer of 1 to 2, and

q is integer of 0 to 2)

(more preferably (1S,4S)-2-aza-5-oxabicyclo[2.2.1]-heptan-2-yl) which may be substituted with one or two lower alkyl (more preferably C<sub>1</sub>-C<sub>4</sub> alkyl, most preferably methyl).

More preferred embodiments of the object compound (I) are as follows:

Y is lower alkylene (more preferably C<sub>1</sub>-C<sub>4</sub> alkylene, most preferably methylene);

R<sup>1</sup> is phenyl which may be substituted with 1 or 2 substituent(s) selected from the group consisting of lower alkoxy, mono(or di or tri)halo(lower)alkyl, lower alkylthio, lower alkylsulfonyl, di(lower alkyl)-aminosulfonyl, pyrrolyl and pyridyl [more preferably bis(trihalo(lower)alkyl)phenyl, (trihalo(lower)alkyl)((lower)alkoxy)phenyl, (trihalo(lower)alkyl)((lower)alkylthio)phenyl, (trihalo(lower)alkyl)((lower)alkylsulfonyl)phenyl, (trihalo(lower)alkyl)(di(lower alkyl)aminosulfonyl)-phenyl, (trihalo(lower)alkyl)(pyrrolyl)phenyl or (trihalo(lower)alkyl)(pyridyl)phenyl, most preferably 3,5-bis(trifluoromethyl)phenyl, 3-methoxy-5-trifluoromethylphenyl, 3-methylthio-5-trifluoromethylphenyl, 3-methylsulfonyl-5-trifluoromethylphenyl, 3-dimethylaminosulfonyl-5-trifluoromethylphenyl, 3-(1-pyrrolyl)-5-trifluoromethylphenyl or 3-(4-pyridyl)-5-trifluoromethylphenyl];

R<sup>2</sup> is phenyl which may be substituted with 1 or 2 substituent(s) selected from the group consisting of lower alkyl, mono(or di or tri)halo(lower)alkyl, halogen, lower alkylenedioxy, lower alkoxy, lower alkoxy(lower)alkoxy(lower)alkoxy, hydroxy, hydroxy(lower)alkyl, cyano, pyrrolidinyl and morpholinyl which may be substituted with lower alkoxy(lower)alkyl or lower alkyl [more preferably (lower)alkylenedioxy)phenyl, halophenyl, [trihalo(lower)alkyl]phenyl, (halo)((lower)alkyl)phenyl, (halo)[(lower)alkoxy]phenyl, (halo)(hydroxy)phenyl,

[trihalo(lower)alkyl](hydroxy)-  
 phenyl, [hydroxy(lower)alkyl](hydroxy)phenyl,  
 (cyano)(hydroxy)phenyl, (dihalo(lower)alkyl)(hydroxy)-  
 phenyl, (lower alkyl)(hydroxy)phenyl, (lower  
 5 alkyl)(pyrrolidinyl)phenyl, (lower  
 alkyl)(morpholinyl)phenyl, (lower alkyl)[(lower)alkoxy-  
 (lower)alkylmorpholinyl]phenyl or (lower alkyl)[(lower  
 alkyl)morpholinyl]phenyl, most preferably 1,4-  
 benzodioxan-6-yl, 4-fluorophenyl, 4-(trifluoromethyl)-  
 10 phenyl, 4-fluoro-3-methylphenyl, 4-fluoro-3-methoxy-  
 phenyl, 3-fluoro-4-methylphenyl, 4-chloro-3-hydroxy-  
 phenyl, 3-hydroxy-4-(trifluoromethyl)phenyl, 3-hydroxy-  
 4-(hydroxymethyl)phenyl, 3-hydroxy-4-methylphenyl, 3-  
 hydroxy-4-(1-hydroxy-1-methylethyl)phenyl, 4-cyano-3-  
 15 hydroxyphenyl, 3-hydroxy-4-(difluoromethyl)phenyl, 3-  
 hydroxy-4-isopropylphenyl, 4-methyl-3-pyrrolidinophenyl  
 or 4-methyl-3-morpholinophenyl] or indolyl;

R<sup>3</sup> is hydrogen; and

R<sup>4</sup> is (2,6-dimethylmorpholino)(lower)alkyl (more preferably  
 20 (2,6-dimethylmorpholino)(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably  
 2-(2,6-dimethylmorpholino)ethyl);  
 (3,3-dimethylmorpholino)(lower)alkyl (more preferably  
 (3,3-dimethylmorpholino)(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably  
 2-(3,3-dimethylmorpholino)ethyl);  
 25 (cis-3,5-dimethylmorpholino)(lower)alkyl (more  
 preferably (cis-3,5-dimethylmorpholino)(C<sub>1</sub>-C<sub>4</sub>)alkyl,  
 most preferably 2-(cis-3,5-dimethylmorpholino)ethyl);  
 ((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl (more  
 preferably ((3S,5S)-3,5-dimethylmorpholino)(C<sub>1</sub>-C<sub>4</sub>)alkyl,  
 30 most preferably 2-((3S,5S)-3,5-dimethylmorpholino)-  
 ethyl);  
 (2-methoxymethylmorpholino)(lower)alkyl (more preferably  
 (2-methoxymethylmorpholino)(C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably  
 3-(2-methoxymethylmorpholino)propyl or  
 35 2-(2-methoxymethylmorpholino)ethyl);



(3-methoxymethylmorpholino) (lower)alkyl (more preferably (3-methoxymethylmorpholino) (C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably 2-(3-methoxymethylmorpholino)ethyl);

(2-methoxymethyl-5-methylmorpholino) (lower)alkyl (more preferably (2-methoxymethyl-5-methylmorpholino) (C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably 2-(2-methoxymethyl-5-methylmorpholino)ethyl);

(2-methoxymethyl-5,5-dimethylmorpholino) (lower)alkyl (more preferably (2-methoxymethyl-5,5-dimethylmorpholino) (C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably 2-(2-methoxymethyl-5,5-dimethylmorpholino)ethyl);

(3,5-dimethoxymethylmorpholino) (lower)alkyl (more preferably (3,5-dimethoxymethylmorpholino) (C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably 2-(3,5-dimethoxymethylmorpholino)ethyl);

(2,3-dimethoxymethylmorpholino) (lower)alkyl (more preferably (2,3-dimethoxymethylmorpholino) (C<sub>1</sub>-C<sub>4</sub>)alkyl, most preferably 2-(2,3-dimethoxymethylmorpholino)ethyl); or (2-methoxymethylmorpholino) (lower)alkenyl (more preferably (2-methoxymethylmorpholino) (C<sub>2</sub>-C<sub>4</sub>)alkenyl, most preferably 4-(2-methoxymethylmorpholino)-2-butenyl).

The Processes 1 and 2 for preparing the object compound (I) of the present invention are explained in detail in the following.

#### Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the imino group or a salt thereof with the compound (III) or a salt thereof.

Suitable reactive derivative at the imino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde,

ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by  
5 reaction of the compound (II) with phosphorus trichloride or phosgene and the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene  
10 chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

The reaction may also be carried out in the presence of an inorganic or organic base such as alkali metal carbonate (e.g. potassium carbonate, etc.), alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkyl-morpholine, N,N-di(lower)alkylethylamine (e.g. N,N-diisopropylethylamine,  
20 etc.), N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

## Process 2

25 The object compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to a reduction reaction.

The reaction can be carried out in the manner disclosed in Example 8 mentioned later or similar manners thereto.

30 The object compound (I) and a pharmaceutically acceptable salt thereof have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism or Neurokinin B antagonism, and  
35 therefore are useful for treating or preventing Tachykinin-

mediated diseases, particularly Substance P-mediated diseases, for example, respiratory diseases such as asthma, bronchitis (e.g. chronic bronchitis, acute bronchitis and diffuse panbronchiolitis, etc.), rhinitis, cough, expectoration, and the like; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like; pains or aches (e.g. migraine, headache, cluster headache, toothache, cancerous pain, back pain, neuralgia, etc.); and the like.

Further, it is expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing ophthalmic diseases such as glaucoma, uveitis, and the like; gastrointestinal diseases such as ulcer, ulcerative colitis, irritable bowel syndrome, food allergy, and the like; inflammatory diseases such as nephritis, and the like; circulatory diseases such as hypertension, angina pectoris, cardiac failure, thrombosis, Raynaud's disease, and the like; epilepsy; spastic paralysis; pollakiuria; cystitis; bladder detrusor hyperreflexia; urinary incontinence; Parkinson diseases; dementia; AIDS related dementia; Alzheimer's diseases; Down's syndrome; Huntington's chorea; carcinoid syndrome; disorders related to immune enhancement or suppression; disorders caused by *Helicobacter pylori* or another spiral urease-positive gram-negative bacterium; sunburn; angiogenesis or diseases caused by angiogenesis; and the like.

It is furthermore expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing chronic

obstructive pulmonary diseases, particularly chronic pulmonary emphysema; iritis; proliferative vitreoretinopathy; psoriasis; inflammatory intestinal diseases, particularly Crohn's diseases; hepatitis; superficial pain on congelation, burn, herpes zoster or diabetic neuropathy; telalgia attended to hyperlipidemia; postoperative neuroma, particularly of mastectomy; vulvar vestibulitis; hemodialysis-associated itching; lichen planus; laryngopharyngitis; bronchiectasis; coniosis; whooping cough; pulmonary tuberculosis; cystic fibrosis; emesis (e.g., nausea, retching, vomiting, acute emesis, delayed emesis, anticipatory emesis, post operative nausea and vomiting (PONV), acute and/or delayed emesis induced by drugs such as cancer chemotherapeutic agents, etc.); mental diseases, particularly anxiety, depression, dysthymic disorders and schizophrenia; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis; attenuation of morphine withdrawal; oedema, such as oedema caused by thermal injury; small cell carcinomas, particularly small cell lung cancer (SCLC); hypersensitivity disorders such as poison ivy; fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; reflex sympathetic dystrophy such as shoulder/hand syndrome; addiction disorders such as alcoholism; stress related somatic disorders; rheumatic diseases such as fibrositis; and the like.

Furthermore, the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are Central Nervous System (CNS) penetrant.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compound, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral, external including topical, enteral,

intravenous, intramuscular, inhalant, nasal, intraarticular, intraspinal, transtracheal or transocular administration.

The pharmaceutical preparations may be solid, semi-solid or solutions such as capsules, tablets, pellets, dragees, powders, granules, suppositories, ointments, creams, lotions, inhalants, injections, cataplasms, gels, tapes, eye drops, solution, syrups, aerosols, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of a patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating Tachykinin-mediated diseases such as asthma and the like. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

In order to show the utility of the object compound (I) and a pharmaceutically acceptable salt thereof, the pharmacological test data of some representative compounds of the present invention is shown in the following.

A. Evaluation of NK<sub>1</sub> antagonist transport efficiency to the central nervous system using a h-NK<sub>1</sub> receptor binding assay

[1] Test Method

(1) Administration of test compound and extraction of the compound from brain

Male SD rats were given an i.v. injection of a solution containing a test compound (1 mg/kg). 5 Min later the animals were anesthetized by ether, bled and perfused through

the aorta ascendens with 20 ml of saline. The brain was rapidly removed, weighed and homogenized in 4 vol. ice-cold distilled water by using Polytoron (KINEMATICA). To extract the test compound, 500  $\mu$ l of the homogenate, 100  $\mu$ l of methanol, 500  $\mu$ l of 0.1 N NaOH and 4 ml of ethyl acetate were mixed by shaking for 10 min at room temperature. The organic phase (2.5 ml) was recovered by centrifugation at 3,000 rpm for 10 min, dried and dissolved in dimethyl sulfoxide.

10 (2) h-NK<sub>1</sub> receptor binding assay

(a) Crude CHO cell membrane preparation

CHO cells permanently expressing h-NK<sub>1</sub> receptors were harvested and homogenized with a Dounce homogenizer at 4°C in a buffer (0.25 M sucrose, 25 mM Tris-HCl (pH 7.4), 10 mM MgCl<sub>2</sub>, 1 mM EDTA, 5  $\mu$ g/ml p-APMSF). The homogenate was centrifuged (500 x g, 10 min), and the pellet was resuspended in the same buffer, homogenized, and centrifuged. The two supernatants were combined and centrifuged (100,000 x g, 1 hour). The crude cell membranes thus isolated were resuspended in a buffer (25 mM Tris-HCl (pH 7.4), 10 mM MgCl<sub>2</sub>, 1 mM EDTA, 5  $\mu$ g/ml p-APMSF) and stored at -80° until use.

25

(b) <sup>125</sup>I-BH-Substance P binding to the prepared membrane

Cell membranes (6  $\mu$ g/ml) were incubated with <sup>125</sup>I-BH-Substance P (0.1 nM) with or without the extracted compounds in 0.25 ml of a medium (50 mM Tris-HCl (pH 7.4), 5 mM MnCl<sub>2</sub>, 20  $\mu$ g/ml chymostatin, 40  $\mu$ g/ml bacitracin, 4  $\mu$ g/ml leupeptin, 5  $\mu$ g/ml p-APMSF, 200  $\mu$ g/ml BSA) at 22°C for 90 min. At the end of the incubation period, the contents were quickly filtered through a Blue Mat 11740 filter (pretreated with 0.1% polyethylenimine for 3 hours prior to use) by using

35

SKATRON Cell Harvester. The filter was then washed with a washing buffer (50 mM Tris-HCl (pH 7.4), 5 mM MnCl<sub>2</sub>). The radioactivity was counted by using an auto gamma counter (Packard RIASTAR 5420A). All data presented are specific binding defined as that displaceable by 3  $\mu$ M unlabeled Substance P.

[II] Test Result

All of the following Test Compounds showed more than 80% inhibition rate of <sup>125</sup>I-BH-Substance P binding to h-NK<sub>1</sub> receptors at the dose of 1 mg/kg.

Test Compounds: The object compounds of the  
Examples 4-(1), 4-(2), 7 and 8

B. Emesis in the dog

[I] Test Method

Individually housed adult female dogs (8 to 15 kg) were given an i.v. injection of a solution containing a test compound. 5 Min later the emetic responses (retching and vomiting) were induced by administration of subcutaneous apomorphine (0.1 mg/0.5 ml/kg) and observed for the next 60 min. The timing and number of retches and vomits observed were recorded for each animal. An individual animal was tested with at least 10 days between experiments.

[II] Test Result

The following Test Compound showed 100% inhibition rate of emesis in the dog at the dose of 0.32 mg/kg.

Test compound: The object compound of the  
Example 4-(1)

The following Preparations and Examples are given for the purpose of illustrating this invention.

#### Preparation 1

(2-Methoxyethoxy)methyl chloride (4.87 ml) was added to a solution of 3-hydroxy-4-methylbenzoic acid (2.16 g) and N,N-diisopropylethylamine (9.2 ml) in 1,2-dichloroethane (40 ml) at room temperature. The mixture was stirred under reflux for 24 hours. After removal of the solvent by evaporation, the residue was partitioned between aqueous diluted hydrochloric acid solution and ethyl acetate. The organic layer was separated and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The crude oil was purified by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (3:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2-methoxyethoxy)methyl 3-[(2-methoxyethoxy)methoxy]-4-methylbenzoate (4.82 g) as an oil.

IR (Neat): 1725, 1595  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.29 (3H, s), 3.37 (3H, s), 3.39 (3H, s), 3.54-3.90 (8H, m), 5.35 (2H, s), 5.60 (2H, s), 7.21 (1H, d,  $J=8.0\text{Hz}$ ), 7.65 (1H, dd,  $J=1.6$  and  $8.0\text{Hz}$ ), 7.74 (1H, d,  $J=1.4\text{Hz}$ )

MASS (API-ES): 351 ( $\text{M}+\text{Na}$ )<sup>+</sup>

#### Preparation 2

Lithium aluminum hydride (0.35 g) was added by small portions over 12 minutes to an ice-cooled solution of (2-methoxyethoxy)methyl 3-[(2-methoxyethoxy)methoxy]-4-methylbenzoate (3.5 g) in tetrahydrofuran (20 ml) below 5°C under nitrogen atmosphere. After the mixture was stirred at the same temperature for 30 minutes, 2N sodium hydroxide (0.5 ml) was added to the mixture. After the mixture was stirred for 30 minutes, the insoluble materials were removed by



filtration and washed with tetrahydrofuran. The filtrate and the washing were combined, and evaporated under reduced pressure. The residue was dissolved into ethyl acetate, and manganese(IV) oxide (3.5 g) was added to the solution. After being stirred under reflux for 2 hours, the reaction mixture was filtered through Celite® and the insoluble mass was washed with ethyl acetate. The filtrate and the washing were combined and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (10:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give 3-[(2-methoxyethoxy)methoxy]-4-methylbenzaldehyde (1.7 g) as an oil.

IR (Neat): 1687, 1407  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.31 (3H, s), 3.38 (3H, s), 3.55-3.60 (2H, m), 3.82-3.87 (2H, m), 5.37 (2H, s), 7.30 (1H, d,  $J=7.7\text{Hz}$ ), 7.44 (1H, dd,  $J=1.4$  and  $7.7\text{Hz}$ ), 7.58 (1H, d,  $J=1.4\text{Hz}$ ), 9.92 (1H, s)

MASS (API-ES): 279 ( $\text{M}+\text{Na}+\text{MeOH}$ )<sup>+</sup>, 247 ( $\text{M}+\text{Na}$ )<sup>+</sup>

### Preparation 3

To a stirred mixture of 3-[(2-methoxyethoxy)methoxy]-4-methylbenzaldehyde (1.70 g) and 1,4-diacetyl-2,5-piperazinedione (1.6 g) in a mixture of N,N-dimethylformamide (17 ml) and tert-butanol (17 ml) was added potassium tert-butoxide (900 mg) at 5°C. The mixture was stirred for 24 hours at room temperature and then poured into water (300 ml). The aqueous mixture was adjusted to pH 4-5 with aqueous diluted hydrochloric acid solution and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using mixed solvents of toluene and ethyl acetate (3:1). The fractions containing the objective compound were

collected and evaporated under reduced pressure to give 1-acetyl-3-[3-[(2-methoxyethoxy)methoxy]-4-methylphenyl]-methylene-2,5-piperazinedione (2.05 g) as a powder.

IR (KBr): 3208, 1700, 1627, 1598, 1455, 1375  $\text{cm}^{-1}$

5 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.26 (3H, s), 2.65 (3H, s), 3.27 (3H, s), 3.58-3.62 (2H, m), 3.81-3.86 (2H, m), 4.49 (2H, s), 5.32 (2H, s), 6.94 (1H, dd,  $J=1.5$  and 7.8Hz), 7.15 (1H, d,  $J=7.8\text{Hz}$ ), 7.23 (1H, d,  $J=1.5\text{Hz}$ ), 7.27 (1H, s), 8.34 (1H, br s)

10 MASS (API-ES): 417 ( $\text{M}+\text{MeOH}+\text{Na}$ )<sup>+</sup>

#### Preparation 4

A solution of 1-acetyl-3-[[3-[(2-methoxyethoxy)methoxy]-4-methylphenyl]methylene]-2,5-piperazinedione (2.0 g) in 15 tetrahydrofuran (20 ml) was hydrogenated over 10% palladium-carbon (50% wet, 0.2 g) at room temperature under atmospheric pressure for 3 hours. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure. The resulting residue was dissolved into 20 tetrahydrofuran (30 ml) and thereto was added hydrazine monohydrate (1.5 ml). After being stirred for 1 hour at room temperature, the mixture was concentrated under reduced pressure. The residue was triturated with isopropyl alcohol and the resulting solid was collected by filtration to give 25 3-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-2,5-piperazinedione (1.75 g).

IR (KBr): 3183, 3060, 1675, 1454  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.21 (3H, s), 2.95-4.00 (8H, m), 3.36 (3H, s), 4.20-4.27 (1H, m), 5.19 (1H, d,  $J=7.0\text{Hz}$ ), 30 5.38 (1H, d,  $J=7.0\text{Hz}$ ), 6.50 (1H, br s), 6.72 (1H, br s), 6.75 (1H, dd,  $J=1.4$  and 7.9Hz), 6.97 (1H, d,  $J=1.4\text{Hz}$ ), 7.08 (1H, d,  $J=7.9\text{Hz}$ )

MASS (APCI): 323 ( $\text{M}+\text{H}$ )<sup>+</sup>, 247, 235

#### 35 Preparation 5

Lithium aluminum hydride (0.62 mg) was added to an ice-cooled solution of 3-[3-[(2-methoxyethoxy)methoxy]-4-methyl]-benzyl-2,5-piperazinedione (1.7 g) in tetrahydrofuran (17 ml) below 5°C under nitrogen atmosphere. The mixture was stirred  
5 under reflux for 3.5 hours. After the mixture was cooled below 5°C, 2N sodium hydroxide was added to the mixture. After the mixture was stirred for 30 minutes at the same temperature, the insoluble materials were removed by filtration and washed with tetrahydrofuran. The filtrate and  
10 the washing were combined and evaporated under reduced pressure. The residue was dissolved into ethyl acetate, and the solution was dried over sodium sulfate and evaporated under reduced pressure to give 2-[3-[(2-methoxyethoxy)-methoxy]-4-methylbenzyl]piperazine (1.27 g) as an oil.

15 A solution of benzyloxycarbonyl chloride (0.75 g) in dichloromethane (1 ml) was added dropwise over 5 minutes to an ice-cooled solution of 2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (1.27 g) obtained by above procedure and triethylamine (2.2 ml) in dichloromethane (10 ml) below  
20 5°C. After the mixture was stirred for 30 minutes at the same temperature, a solution of 3,5-bis(trifluoromethyl)-benzoyl chloride (0.93 ml) in dichloromethane (1.0 ml) was added dropwise to the mixture over 10 minutes below 5°C. After being stirred for 30 minutes at the same temperature,  
25 the reaction mixture was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of toluene and ethyl acetate (5:1). The fractions containing the objective compound were collected  
30 and evaporated under reduced pressure to give 1-[3,5-bis(trifluoromethyl)benzoyl]-4-(benzyloxycarbonyl)-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (1.61 g) as an oil.

IR (Neat): 2879, 1700, 1645  $\text{cm}^{-1}$

35 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.19 (3H, s), 3.35 (3H, s), 2.40-5.40

(17H, m), 6.40-8.10 (10H, m), 7.82 (1H, br s)  
MASS (APCI): 669 (M+H)<sup>+</sup>

#### Preparation 6

5 A solution of 1-[3,5-bis(trifluoromethyl)benzoyl]-4-(benzyloxycarbonyl)-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (1.6 g) in methanol (20 ml) was hydrogenated over 10% palladium-carbon (50% wet, 0.2 g) at room temperature under atmospheric pressure for 4 hours.  
10 After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (40:1). The fractions containing the objective compound were collected  
15 and evaporated under reduced pressure to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (0.89 g) as an oil.

IR (Neat): 1732, 1714, 1705, 1647, 1431 cm<sup>-1</sup>

20 NMR (CDCl<sub>3</sub>, δ): 2.20 (3H, s), 2.50-5.20 (16H, m), 3.00 (3H, s), 6.40-7.40 (5H, m), 7.80 (1H, s)

MASS (API-ES): 557 (M+Na)<sup>+</sup>, 535 (M+H)<sup>+</sup>

#### Preparation 7

25 To a mixed solution of (3R)-3-(methoxymethyl)morpholine hydrochloride (4.71 g) and triethylamine (4.11 ml) in methanol (110 ml) was added 5.8M ethylene oxide (22 ml) in toluene solution at room temperature. After the reaction mixture was stirred at the same temperature for two days, it was evaporated under reduced pressure. The residue was  
30 purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (20:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give 2-[(3R)-3-methoxymethylmorpholino]ethanol (4.67 g) as an oil.

35 IR (Neat): 3433, 2860, 1454, 1119, 1055 cm<sup>-1</sup>

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.38-3.05 (5H, m), 3.33 (3H, s),  
3.40-3.80 (8H, m)  
MASS (APCI): 176 (M+H)<sup>+</sup>

5     Preparation 8

The following compounds were obtained according to a similar manner to that of Preparation 8.

(1) 2-[cis-2,6-Dimethylmorpholino]ethanol

10     IR (Neat): 3431, 3402, 1456, 1373, 1325, 1146  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.17 (6H, d, J=6.3Hz), 1.84 (2H, dd, J=10.2 and 11.4Hz), 2.52 (2H, t, J=5.5Hz), 2.71-2.78 (2H, m), 3.65 (2H, t, J=5.6Hz), 3.49-3.76 (2H, m)  
15     MASS (APCI): 160 (M+H)<sup>+</sup>

(2) 2-[(2S,5S)-2-Methoxymethyl-5-methylmorpholino]ethanol

IR (Neat): 3433, 3400, 1456, 1379, 1327, 1086, 1051  $\text{cm}^{-1}$   
20     NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.19 (3H, d, J=6.3Hz), 1.88 (1H, d, J=10.8Hz), 1.96 (1H, t, J=10.5Hz), 2.54 (2H, t, J=5.5Hz), 2.72-2.83 (2H, m), 3.38 (3H, s), 3.36-3.45 (2H, m), 3.63 (2H, t, J=5.2Hz), 3.60-3.90 (2H, m)  
25     MASS (APCI): 190 (M+H)<sup>+</sup>

(3) 2-[(2S)-2-(Methoxymethyl)morpholino]ethanol

IR (Neat): 3435, 1456, 1354, 1302  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.06 (1H, t, J=10.7Hz), 2.27 (1H, td, J=10.7 and 3.3Hz), 2.53-2.58 (2H, m), 2.68-2.84 (2H, m), 3.38 (3H, s), 3.38-3.44 (2H, m), 3.61-3.75 (4H, m), 3.89-3.98 (1H, m)  
30     MASS (API-ES): 176 (M+H)<sup>+</sup>, 198 (M+Na)<sup>+</sup>

35     Preparation 9

To an ice-cooled solution of 2-[(3R)-3-methoxymethylmorpholino]ethanol (505 mg) in toluene (2.5 ml) was added dropwise a solution of thionyl chloride (429 mg) in toluene (1.5 ml) below 5°C under nitrogen atmosphere. The mixture was stirred at 70°C for 1.5 hours. After the mixture was cooled at room temperature, ethyl acetate was added to the mixture, and resulting suspension was evaporated under reduced pressure. Diisopropyl ether was added to the residue, and after the mixture was stirred at room temperature for 15 minutes, the resulting precipitates were collected by filtration, washed with diisopropyl ether and dried at 40°C under reduced pressure to give (3R)-4-(2-chloroethyl)-3-(methoxymethyl)morpholine hydrochloride (620 mg) as a light yellowish powder.

mp: 162-163°C

IR (KBr): 2945, 1140, 1109, 1084  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 3.31 (3H, s), 3.10-4.10 (13H, m)

MASS (APCI): 194 (M+H)<sup>+</sup> (free)

#### Preparation 10

The following compounds were obtained according to a similar manner to that of Preparation 9.

(1) cis-2,6-Dimethyl-4-(2-chloroethyl)morpholine hydrochloride

IR (KBr): 1513, 1458, 1394, 1336, 1143  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.12 (6H, d, J=6.3Hz), 2.60-2.80 (2H, m), 3.44-3.50 (4H, m), 3.95-4.10 (4H, m)

MASS (APCI): 178 (M+H)<sup>+</sup> (free)

(2) (2S,5S)-4-(2-Chloroethyl)-2-methoxymethyl-5-methylmorpholine hydrochloride

IR (KBr): 2613, 1456, 1390, 1124, 1082  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.13 (3H, d, J=6.3Hz), 2.50-3.00

(3H, m), 3.27 (3H, s), 3.34-3.51 (7H, m), 4.03-4.10

(4H, m)

MASS (APCI): 208 (M+H)<sup>+</sup> (free)

(3) (2S)-4-(2-Chloroethyl)-2-(methoxymethyl)morpholine  
hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 3.00 (2H, m), 3.27 (3H, s), 3.47  
(4H, m), 3.75-4.12 (7H, m), 11.91 (1H, m)

MASS (APCI): 194 (M+H)<sup>+</sup> (free)

#### 10 Preparation 11

Sodium triacetoxymethylborohydride (36.7 g) was added  
portionwisely to a mixture of (2S)-2-amino-1-propanol (10.0  
g) and benzaldehyde (13.53 ml) in a mixture of  
dichloromethane (140 ml) and acetic acid (8.38 ml) at 0°C and  
the whole was stirred at room temperature overnight. The  
mixture was washed successively with 2N sodium hydroxide and  
brine, and dried over sodium sulfate. The solution was  
evaporated under reduced pressure and the resulting residue  
was purified by column chromatography on silica gel using a  
mixed solvent of dichloromethane and methanol (30:1). The  
fractions containing the objective compound were collected  
and evaporated under reduced pressure to give (2S)-2-  
benzylamino-1-propanol (15.96 g).

IR (KBr): 2843, 1496, 1454, 1377, 1340, 1065 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ): 1.10 (3H, d, J=6.4Hz), 2.77-2.93 (1H,  
m), 3.28 (1H, dd, J=10.6 and 6.9Hz), 3.61 (1H, dd,  
J=10.6 and 4.0Hz), 3.75, 3.87 (2H, ABq, J=13Hz),  
7.21-7.34 (5H, m)

MASS (API-ES): 166 (M+H)<sup>+</sup>

#### 30 Preparation 12

(s)-(+)-Methyl glycidyl ether (8.25 ml) was added  
dropwise to a solution of (2S)-2-benzylamino-1-propanol (7.6  
g) in methanol (7.6 ml) at room temperature. After being  
stirred at 40-50° for 24 hours, the solution was concentrated

under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (30:1). The fractions containing the objective compound were collected and  
5 evaporated under reduced pressure to give (2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-methoxypropyl]amino]-1-propanol (10.4 g) as an oil.

IR (Neat): 3400, 2929, 1452, 1414, 1373, 1329  $\text{cm}^{-1}$

10 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.96 (3H, d,  $J=6.7\text{Hz}$ ), 2.50-2.60 (1H, m), 2.57 (1H, dd,  $J=13.4$  and  $6.2\text{Hz}$ ), 2.67 (1H, dd,  $J=13.4$  and  $6.5\text{Hz}$ ), 2.95-3.10 (1H, m), 3.21-3.52 (4H, m), 3.30 (3H, s), 3.49 (1H, d,  $J=13.6\text{Hz}$ ), 3.71-3.75 (1H, m), 3.83 (1H, d,  $J=13.6\text{Hz}$ ), 7.21-7.37 (5H, m)

15 MASS (APCI): 254  $(\text{M}+\text{H})^+$

### Preparation 13

Triphenylphosphine (10.09 g) was added to a solution of (2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-methoxypropyl]amino]-1-propanol (8.86 g) in tetrachloromethane (4.06 ml) at room  
20 temperature. After being stirred at room temperature for 2 days, the solution was concentrated under reduced pressure. The residue was triturated with diisopropyl ether (200 ml) three times, and the soluble portions were separated by  
25 decantation and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (40:1). The fractions containing the objective compound were  
30 collected and evaporated under reduced pressure to give (2S)-1-[N-benzyl-N-[(1S)-2-chloro-1-methylethyl]amino]-3-methoxy-2-propanol (4.90 g) as an oil.

IR (Neat): 3463, 1452, 1362  $\text{cm}^{-1}$

35 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.43 (3H, d,  $J=6.6\text{Hz}$ ), 2.53-2.82 (4H, m), 3.30-3.39 (2H, m), 3.36 (3H, s), 3.59 (1H, d,  $J=13.6\text{Hz}$ ), 3.83 (1H, d,  $J=13.6\text{Hz}$ ), 3.79-3.87 (1H,



m), 4.01-4.09 (1H, m), 7.21-7.33 (5H, m)  
MASS (APCI): 272 (M+H)<sup>+</sup>

#### Preparation 14

5 A solution of (2S)-1-[N-benzyl-N-[(1S)-2-chloro-1-methylethyl]amino]-3-methoxy-2-propanol (1.90 g) in N,N-dimethylformamide (10 ml) was added to an ice-cooled suspension of sodium hydride (0.45 g, 60% in mineral oil) in N,N-dimethylformamide (10 ml) at 0°C. After being stirred  
10 for 1 hour at the same temperature, the mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified  
15 by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (10:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2S,5S)-4-benzyl-2-methoxymethyl-5-methylmorpholine (0.86 g) as an oil.

IR (Neat): 2875, 1452, 1362, 1325, 1130, 1082 cm<sup>-1</sup>  
20 NMR (CDCl<sub>3</sub>, δ): 1.15 (3H, d, J=6.3Hz), 1.73-1.93 (2H, m), 2.68-2.77 (2H, m), 3.35 (3H, s), 3.49 (2H, s), 3.31-3.49 (2H, m), 3.68-3.81 (2H, m), 7.25-7.32 (5H, m)  
MASS (APCI): 236 (M+H)<sup>+</sup>

25

#### Preparation 15

A solution of (2S,5S)-4-benzyl-2-methoxymethyl-5-methylmorpholine (0.86 g) in a mixture of concentrated hydrochloric acid (0.31 ml) and methanol (8.6 ml) was  
30 hydrogenated over 10% palladium-carbon (50% wet, 0.2 g) at room temperature under atmospheric pressure for 3 hours. After removal of the catalyst by filtration through Celite<sup>®</sup>, the filtrate was concentrated under reduced pressure to give (2S,5S)-2-methoxymethyl-5-methylmorpholine hydrochloride  
35 (0.71 g) as an oil.

IR (Neat): 3433, 3402, 2939, 1597, 1456, 1392, 1331,  
1107  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 1.12 (3H, d,  $J=6.3\text{Hz}$ ), 2.49-2.75  
(2H, m), 3.13-3.19 (2H, m), 3.27 (3H, s), 3.38 (2H,  
5 d,  $J=4.8\text{Hz}$ ), 3.80-4.00 (2H, m)

MASS (APCI): 146 ( $\text{M}+\text{H}$ )<sup>+</sup> (free)

#### Preparation 16

N-Acetyl-3-methoxy-4-methyl-DL-phenylalanine (7.28 g)  
10 was dissolved into a mixture of water (36.5 ml) and 1N sodium  
hydroxide solution (29 ml). Cobalt(II) chloride hexahydrate  
(36.5 mg) and acylase (Acylase Amano, 365 mg) were added to  
the solution and the mixture was stirred at 37°C for 15.5  
hours with controlling the pH of the reaction mixture to 7.5  
15 with 1N sodium hydroxide solution. The insoluble material  
was removed by filtration and the pH of the filtrate was made  
to 3 with 6N hydrochloric acid, extracted with ethyl acetate,  
washed with water, dried over sodium sulfate, and evaporated  
in vacuo to give crude N-acetyl-3-methoxy-4-methyl-D-  
20 phenylalanine (3.17 g). The crude product was again  
subjected to the acylase reaction (cobalt(II) chloride  
hexahydrate 15.2 mg, acylase 152 mg, 37°C, pH 7.5, 20 hours)  
to give pure N-acetyl-3-methoxy-4-methyl-D-phenylalanine  
(2.70 g) as a viscous oil.

25  $[\alpha]_D^{26.8}$ : -36.16° ( $C=0.424$ , MeOH)

IR (Neat): 3350, 1740, 1725  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.99 (3H, s), 2.17 (3H, s), 3.00-3.30  
(2H, m), 3.78 (3H, s), 4.75-4.90 (1H, m), 6.00-7.10  
(3H, m), 6.36 (2H, br s)

30 MASS (APCI): 252 ( $\text{M}+\text{H}$ )<sup>+</sup>

#### Preparation 17

A mixture of N-acetyl-3-methoxy-4-methylphenyl-D-alanine  
(2.55 g) in a mixture of 6N hydrochloric acid (25.5 ml) and  
35 toluene (18 ml) was stirred under reflux for 4 hours. After

being cooled to room temperature, the aqueous layer was separated and the organic layer was washed with water (10 ml) twice. The aqueous layer and the washings were combined and evaporated under reduced pressure. The resulting crystals were collected by filtration and washed with ice-water to give 3-methoxy-4-methyl-D-phenylalanine hydrochloride (1.35 g) as colorless crystals. The filtrate was evaporated under reduced pressure to give crude 3-methoxy-4-methyl-D-phenylalanine hydrochloride (0.6 g).

mp: 207-211°C

$[\alpha]_D^{27.2}$ : +20.2° (C=0.5, H<sub>2</sub>O)

IR (KBr): 1735, 1610, 1508 cm<sup>-1</sup>

NMR (D<sub>2</sub>O, δ): 2.18 (3H, s), 3.17 (1H, dd, J=7.6 and 14.6Hz), 3.32 (1H, dd, J=6.0 and 14.6Hz), 3.85 (3H, s), 4.27 (1H, dd, J=6.0 and 7.0Hz), 6.85 (1H, d, J=7.3Hz), 6.91 (1H, s), 7.21 (1H, d, J=8.0Hz)

MASS (APCI): 210 (M+H)<sup>+</sup> (free)

#### Preparation 18

Thionyl chloride (0.7 ml) was added dropwise to a solution of 3-methoxy-4-methyl-D-phenylalanine hydrochloride (1.75 g) in methanol (8 ml) over 10 minutes at room temperature. The whole was stirred at 40-50°C for 2 hours and then an additional thionyl chloride (0.7 ml) was added to the mixture. The whole mixture was stirred for further 1 hour and evaporated under reduced pressure. The resulting solid was triturated with diisopropyl ether and collected by filtration to give colorless crystals of 3-methoxy-4-methyl-D-phenylalanine methyl ester hydrochloride (1.70 g).

mp: 196-197°C

$[\alpha]_D^{30}$ : -4.60° (C=0.5, MeOH)

IR (Nujol): 3400, 1741, 1583, 1465, 1446, 1249 cm<sup>-1</sup>

NMR (D<sub>2</sub>O, δ): 2.19 (3H, s), 3.21 (1H, dd, J=7.4 and 14.5Hz), 3.32 (1H, dd, J=6.0 and 14.5Hz), 3.85 (6H, s), 4.43 (1H, dd, J=6.0 and 7.4Hz), 6.82 (1H, dd,

$J=1.4$  and  $7.6\text{Hz}$ ),  $6.87$  (1H, d,  $J=1.4\text{Hz}$ ),  $7.22$  (1H, d,  $J=7.6\text{Hz}$ )

MASS (APCI):  $224$  (M+H)<sup>+</sup> (free),  $207$ ,  $164$

5 Preparation 19

Potassium carbonate (1.70 g) was added by small portions with ice-cooling to a mixture of 3-methoxy-4-methyl-D-phenylalanine methyl ester hydrochloride (1.60 g) in mixed solvents of dichloromethane (7 ml) and water (9 ml).

10 Chloroacetyl chloride (0.66 ml) was added to the mixture below  $5^{\circ}\text{C}$  over 15 minutes and then the whole was stirred for 30 minutes. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give an oil of (2R)-2-[N-(chloroacetyl)-amino]-3-(3-methoxy-4-methylphenyl)propionic acid methyl ester.

IR (Neat):  $3305$ ,  $1737$ ,  $1643$ ,  $1583\text{ cm}^{-1}$

Preparation 20

20 Benzylamine (1.65 g) and potassium carbonate (1.28 g) were added successively to a solution of (2R)-2-[N-(chloroacetyl)amino]-3-(3-methoxy-4-methylphenyl)propionic acid methyl ester (1.85 g) in N,N-dimethylformamide (15 ml) at  $20^{\circ}\text{C}$ . After being stirred at  $35^{\circ}\text{C}$  for 1.5 hours, the mixture was poured into a mixture of ice-water (20 ml) and dichloromethane (20 ml). After the mixture was adjusted to pH 9 with diluted aqueous hydrochloric acid under stirring, the organic layer was separated, washed with brine (20 ml), dried over magnesium sulfate and evaporated under reduced pressure to give an oil of (2R)-2-[N-(benzylaminoacetyl)-amino]-3-(3-methoxy-4-methylphenyl)propionic acid methyl ester. A solution of (2R)-2-[N-(benzylaminoacetyl)amino]-3-(3-methoxy-4-methylphenyl)propionic acid methyl ester obtained by above procedure and acetic acid (0.18 ml) in isopropyl alcohol (10 ml) was stirred for 12 hours under

reflux.

After the mixture was cooled to room temperature, isopropyl ether was added to the mixture. The resulting precipitates were collected by filtration and washed with isopropyl ether to give colorless crystals of (3R)-1-benzyl-3-(3-methoxy-4-methylphenyl)piperazine-2,5-dione (1.45 g).

mp: 205-209°C

$[\alpha]_D^{30}$ : +11.12° (C=0.4, DMF)

IR (KBr): 3237, 1677, 1656, 1465, 1446, 1442 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 2.08 (3H, s), 2.76 (1H, d, J=17.2Hz), 2.87 (1H, dd, J=4.8 and 13.4Hz), 3.11 (1H, dd, J=4.8 and 13.4Hz), 3.46 (1H, d, J=17.2Hz), 3.69 (3H, s), 4.25 (1H, d, J=14.6Hz), 4.20-4.30 (1H, m), 4.52 (1H, d, J=14.6Hz), 6.54 (1H, dd, J=1.4 and 7.4Hz), 6.69 (1H, d, J=1.4Hz), 6.87 (1H, d, J=7.4Hz), 7.04-7.11 (2H, m), 7.24-7.30 (3H, m), 8.33 (1H, d, J=2.2Hz)

MASS (APCI): 339 (M+H)<sup>+</sup>

## Preparation 21

Lithium aluminum hydride (0.378 g) was added to an ice-cooled suspension of (3R)-1-benzyl-3-(3-methoxy-4-methylphenyl)-2,5-piperazinedione (1.35 g) in tetrahydrofuran (22 ml) below 5°C under nitrogen atmosphere. The mixture was stirred under reflux for 3 hours. After the mixture was cooled below 5°C, 2N sodium hydroxide was added to the mixture. After the mixture was stirred for 30 minutes, the insoluble materials were removed by filtration and washed with tetrahydrofuran. The filtrate and the washing were combined and evaporated under reduced pressure to give (3R)-1-benzyl-3-(3-methoxy-4-methylphenyl)piperazine as an oil. A solution of 3,5-bis(trifluoromethyl)benzoyl chloride (0.80 ml) in dichloromethane (1 ml) was added dropwise over 5 minutes to an ice-cooled solution of (3R)-1-benzyl-3-(3-methoxy-4-methylphenyl)piperazine obtained by above procedure

and triethylamine (0.84 ml) in dichloromethane (10 ml) below 5°C. After being stirred for 30 minutes at the same temperature, the reaction mixture was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (4:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-methoxy-4-methylbenzyl)piperazine (1.92 g) as an oil.

IR (Neat): 2950, 2850, 1640, 1590, 1515  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.16 (3H, s), 2.00-5.20 (14H, m), 6.25-6.32 (1H, m), 6.70-6.90 (2H, m), 7.20-7.44 (7H, m), 7.80 (1H, br s)

MASS (APCI): 551 ( $\text{M}+\text{H}^+$ ), 573 ( $\text{M}+\text{Na}^+$ )

#### Preparation 22

A solution of boron tribromide in dichloromethane (1M solution, 3.7 ml) was added dropwise over 20 minutes to an ice-cooled solution of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-methoxy-4-methylbenzyl)piperazine (0.68 g) in dichloromethane (5 ml). After being stirred at the same temperature for 2 hours, followed by further stirring at room temperature for 12 hours, the mixture was poured into aqueous saturated sodium hydrogen carbonate solution. The organic layer was separated, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (4:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)piperazine (0.56 g) as a red foam.

IR (Neat): 1630, 1430  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.00-5.20 (14H, m), 5.61 (1H, br s),

6.20-6.25 (1H, m), 6.60-7.70 (2H, m), 7.20-7.60  
(7H, m), 7.80-7.85 (1H, m)

MASS (API-ES): 519 (M-H<sub>2</sub>O+H)<sup>+</sup>, 537 (M+H)<sup>+</sup>, 559 (M+Na)<sup>+</sup>

5 Preparation 23

Sodium hydride (60% in mineral oil, 18 mg) was added by small portions to an ice-cooled solution of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)piperazine (0.20 g) in N,N-dimethylformamide (2 ml) below 5°C under nitrogen atmosphere. After the mixture was stirred for 5 minutes, (2-methoxyethoxy)methyl chloride (0.064 ml) was added to the mixture. The whole was stirred at room temperature for 2.5 hours, and thereto water was added. The whole was extracted with ethyl acetate. The extract was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (7:3). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (0.21 g) as an oil.

IR (Neat): 2950, 1645, 1435 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ): 2.19 (3H, s), 3.34 (3H, s), 2.00-5.20 (17H, m), 6.60-7.40 (10H, m), 7.70-7.80 (1H, m)

MASS (API-ES): 625 (M+H)<sup>+</sup>, 647 (M+Na)<sup>+</sup>

Preparation 24

A mixture of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (0.38 g) in methanol (6 ml) was hydrogenated over 20% palladium hydroxide-carbon (0.06 g) at room temperature under atmospheric pressure for 8 hours. After removal of the catalyst by filtration through Celite<sup>®</sup>, the filtrate was concentrated under reduced pressure. The residue was

purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (30:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (0.32 g) as an oil.

IR (KBr): 3000-2700, 1629, 1513, 1444  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.20 (3H, s), 2.50-5.30 (16H, m), 3.36 (3H, s), 6.40-7.50 (5H, m), 7.80 (1H, s)

MASS (API-ES): 535 (M+H)<sup>+</sup>, 557 (M+Na)<sup>+</sup>

#### Example 1

To a solution of 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (440 mg) in N,N-dimethylformamide (2.2 ml) were added (3R)-4-(2-chloroethyl)-3-(methoxymethyl)morpholine hydrochloride (289 mg), potassium carbonate (434 mg) and potassium iodide (149 mg) at room temperature. The whole was stirred at 73°C for 2 hours. After being cooled to room temperature, the mixture was poured into ice-water and the aqueous mixture was made alkaline with saturated aqueous sodium hydrogen carbonate solution. The resulting mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (40:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-4-[2-[(3R)-3-methoxymethyl-morpholino]ethyl]piperazine (450 mg) as a light yellowish oil.

IR (Neat): 2879, 1639, 1437, 1281, 1136, 1009  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.20 (3H, s), 1.95-5.40 (34H, m), 6.40-8.10 (6H, m)



MASS (APCI): 692 (M+H)<sup>+</sup>

### Example 2

The following compounds were obtained according to a similar manner to that of Example 1.

(1) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-2-[3-[(2-methoxyethoxy)-methoxy]-4-methylbenzyl]piperazine

IR (Neat): 1680, 1643, 1508, 1435 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ): 1.17 (6H, d, J=6.3Hz), 1.78 (2H, t, J=10.8Hz), 2.20 (3H, br s), 2.20-5.30 (23H, m), 3.36 (3H, s), 6.42-8.02 (6H, m)

MASS (APCI): 676 (M+H)<sup>+</sup>

(2) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-4-[2-[(2S,5S)-2-methoxymethyl-5-methylmorpholino]ethyl]piperazine

IR (Neat): 2933, 2881, 1643, 1439, 1281, 1086, 1012 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ): 1.18 (3H, d, J=6.2Hz), 1.78-1.96 (2H, m), 2.20 (3H, br s), 2.20-5.30 (25H, m), 3.37 (3H, s), 3.36 (3H, s), 6.66-7.80 (6H, m)

MASS (API-ES): 706.3 (M+H)<sup>+</sup>, 728.3 (M+Na)<sup>+</sup>

### Example 3

1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-4-[2-[(3R)-3-(methoxymethyl)morpholino]ethyl]piperazine (430 mg) was dissolved in methanol (10 ml) at room temperature, and methanesulfonic acid (0.215 ml) was added to the solution. After being stirred at the same temperature for 18 hours, the reaction mixture was concentrated until one third of original volume under reduced pressure, and poured into iced water. The aqueous mixture was made alkaline with 15% aqueous sodium

hydroxide solution, and the resulting mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (30:1). The fractions containing the objective compound were collected and evaporated under reduced pressure, and the residue was treated with 4N hydrogen chloride in ethyl acetate solution to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-hydroxy-4-methylbenzyl]-4-[2-[(3R)-3-(methoxymethyl)-morpholino]ethyl]piperazine dihydrochloride (280 mg) as a colorless powder.

mp: 167-172°C

$[\alpha]_D^{28}$ : -8.50° (C=0.20, MeOH)

IR (KBr): 3400, 1645, 1429, 1282, 1184, 1138 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 2.08 (3H, s), 2.60-5.10 (25H, m), 6.18-7.10 (3H, m), 7.36-8.22 (3H, m), 9.25 (1H, br)

MASS (APCI): 604 (M+H)<sup>+</sup> (free)

#### Example 4

The following compounds were obtained according to a similar manner to that of Example 3.

(1) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine dihydrochloride

mp: 188-200°C

$[\alpha]_D^{29}$ : +0.70° (C=0.25, MeOH)

IR (KBr): 3402, 1643, 1516, 1429 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 1.15 (6H, d, J=6.0Hz), 2.08 (3H, br s), 2.00-5.10 (19H, m), 6.19-8.21 (6H, m)

MASS (APCI): 588 (M+H)<sup>+</sup> (free)

(2) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[2-[(2S,5S)-2-methoxymethyl-5-

methylmorpholino]ethyl]piperazine dihydrochloride

mp: 214-218°C

$[\alpha]_D^{29}$ : +0.80° (C=0.25, MeOH)

IR (KBr): 3433, 3398, 1645, 1516, 1429, 1371, 1281,  
1182, 1140 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 1.16 (3H, d, J=6.0Hz), 2.08 (3H, br s), 2.50-5.10 (21H, m), 3.27 (3H, s), 6.20-8.20 (6H, m), 9.00-9.20 (1H, m)

MASS (APCI): 618 (M+H)<sup>+</sup> (free)

(3) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzoy)-4-[3-(3-pyridyl)-2-propynyl]piperazine

NMR (CDCl<sub>3</sub>, δ): 0.60-5.30 (14H, m), 5.77 (1H, br s),  
6.20-8.90 (10H, m)

MASS (APCI): 562 (M+H)<sup>+</sup>

#### Example 5

The following compounds were obtained according to a similar manner to that of Example 1 and then a similar manner to that of Example 3.

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine dihydrochloride

mp: 207-210°C

$[\alpha]_D^{26.2}$ : -6.40° (C=0.4, MeOH)

IR (KBr): 3300, 3000, 2700, 1644, 1428 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 2.18 (3H, s), 2.20-5.20 (22H, m),  
6.10-8.20 (6H, m), 9.00-9.40 (1H, br s), 11.00-  
12.00 (2H, m)

MASS (APCI): 604 (M+H)<sup>+</sup> (free)

(2) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine dihydrochloride

IR (KBr): 1645, 1516, 1458, 1425, 1369  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.08 (3H, br s), 3.28 (3H, br s),  
2.40-5.10 (22H, m), 6.19-8.22 (6H, m)

MASS (APCI): 604  $(\text{M}+\text{H})^+$  (free)

5

#### Example 6

A mixture of 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-  
[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (0.4 g),  
1-chloro-3-(3-pyridyl)-2-propyne hydrochloride (0.17 g),  
10 potassium carbonate (0.52 g) and a trace of potassium iodide  
in N,N-dimethylformamide (7 ml) was stirred for 4 hours at  
80°C. After cooling, the solvent was removed by evaporation,  
and ethyl acetate and aqueous sodium hydrogen carbonate  
solution were added thereto. The organic layer was  
15 separated, dried over magnesium sulfate, and evaporated under  
reduced pressure. The residue was purified by column  
chromatography on silica gel using ethyl acetate. The  
fractions containing the objective compound were collected  
and evaporated under reduced pressure to give 1-[3,5-  
20 bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-  
4-methylbenzyl]-4-[3-(3-pyridyl)-2-propynyl]piperazine (0.44  
g) as an oil.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.60-5.60 (23H, m), 6.30-8.90 (10H, m)

MASS (APCI): 650  $(\text{M}+\text{H})^+$

25

#### Example 7

A solution of 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-  
hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)-2-propynyl]-  
piperazine (0.11 g) in methanol (10 ml) was treated with 4N  
30 hydrogen chloride in ethyl acetate (1 ml) and the mixture was  
evaporated under reduced pressure. The residue was  
trituated with a mixture of dichloromethane and ethyl  
acetate and the resulting powder was collected by filtration  
to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-  
35 methylbenzyl)-4-[3-(3-pyridyl)-2-propynyl]piperazine

dihydrochloride (0.07 g).

mp: 180-190°C

IR (KBr): 1693, 1676, 1645, 1549, 1531, 1516, 1460,  
1456, 1427, 1392, 1367, 1317, 1281, 1217, 1188,  
1066 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 1.60-5.20 (14H, m), 6.10-9.00 (10H, m)

MASS (APCI): 562 (M+H)<sup>+</sup> (free)

#### Example 8

A solution of 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)-2-propynyl]-piperazine (0.16 g) in a mixed solvent of methanol (10 ml) and tetrahydrofuran (10 ml) was hydrogenated over 10% palladium-charcoal (20 mg) at room temperature for 1.5 hours. After removal of catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate as an eluent. The fractions containing the objective compound were collected and evaporated under reduced pressure and the resulting residue was treated with 4N hydrogen chloride in ethyl acetate to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)propyl]piperazine dihydrochloride (0.17 g) as a colorless solid.

mp: 60-70°C

IR (KBr): 1707, 1693, 1676, 1645, 1628, 1558, 1550,  
1541, 1516, 1466, 1456, 1427, 1387, 1365, 1329,  
1319, 1281, 1182, 1136, 1039 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 1.80-5.20 (18H, m), 6.00-9.00 (10H, m)

MASS (APCI): 566 (M+H)<sup>+</sup> (free)

#### Preparation 25

A solution of 3-methoxy-p-toluic acid (45.32 g) in tetrahydrofuran (280 ml) was added to a suspension of sodium borohydride (9.29 g) in tetrahydrofuran (45 ml) with ice bath

cooling under nitrogen atmosphere. After 10 minutes stirring, boron trifluoride diethyl etherate (41.5 ml) was added to the mixture at 3 to 15°C and the whole was stirred at room temperature overnight. Water (210 ml) and diisopropyl ether (60 ml) were added to the mixture. The organic layer was separated and the aqueous layer was extracted with diisopropyl ether (100 ml). The combined organic layer was washed successively with 1N sodium hydroxide solution and brine, dried over sodium sulfate, and evaporated in vacuo to give 3-methoxy-4-methylbenzylalcohol (41.63 g) as an oil.

IR (Neat): 3330, 1615, 1590, 1510, 1465, 1418, 1255  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.70 (1H, br s), 2.21 (3H, s), 3.84 (3H, s), 4.65 (2H, s), 6.80-7.16 (3H, m)

#### Preparation 26

A mixture of 3-methoxy-4-methylbenzylalcohol (41.61 g), conc. hydrochloric acid (125 ml) and toluene (83 ml) was stirred at 90°C for 1 hour. After cooling, ice-water (125 ml) and diisopropyl ether (80 ml) were added to the mixture, and the organic layer was separated, and the aqueous layer was extracted with diisopropyl ether (160 ml). The combined organic layer was washed with saturated sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and evaporated in vacuo to give 3-methoxy-4-methylbenzyl chloride (46.35 g) as an oil.

IR (Neat): 1615, 1590, 1510, 1470, 1415, 1255  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.21 (3H, s), 3.85 (3H, s), 4.57 (2H, s), 6.82-7.15 (3H, m)

#### Preparation 27

3-Methoxy-4-methylbenzyl chloride (46.35 g) and ethyl acetamidomalonate (71.16 g) were added successively into a solution of sodium ethoxide (24.34 g) in ethanol (230 ml). The mixture was stirred under reflux for 2 hours, poured into

ice-water (690 ml) and the pH of the mixture was adjusted to 7 with 6N hydrochloric acid. The resulting precipitates were collected by filtration, washed with aqueous ethanol (3:1, 100 ml) and dried to give crude 2-acetylamino-2-(3-methoxy-4-methylbenzyl)malonic acid diethyl ester (85.03 g). A suspension of the crude product (80.66 g) in heptane (400 ml) was stirred at 50°C for 1 hour and cooled to room temperature. The resulting precipitates were collected by filtration, washed with heptane, and dried to give pure product (74.57 g) as a colorless crystals.

mp: 123-125°C

IR (KBr): 3251, 1747, 1643, 1518, 1267, 1213, 1190, 1051  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.30 (6H, t,  $J=7.1\text{Hz}$ ), 2.03 (3H, s), 2.16 (3H, s), 3.61 (2H, s), 3.76 (3H, s), 4.28 (4H, q,  $J=7.1\text{Hz}$ ), 6.44-7.06 (4H, m)

#### Preparation 28

A mixture of 2-acetylamino-2-(3-methoxy-4-methylbenzyl)-malonic acid diethyl ester (10.0 g), potassium hydroxide solution (1.88 g) in water (25 ml) and ethanol (25 ml) were stirred under reflux for 1 hour. Another potassium hydroxide solution (1.88 g) in water (10 ml) was added to the mixture and the whole was stirred under reflux for 2 hours. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure. Water (50 ml) and ethyl acetate (50 ml) were added to the resulting aqueous solution. The aqueous layer was separated and was adjusted to pH 1.5 with 6N hydrochloric acid. The solution was extracted with ethyl acetate, washed with brine, dried over sodium sulfate and evaporated under reduced pressure to give N-acetyl-3-methoxy-4-methyl-DL-phenylalanine (7.58 g) as a viscous oil.

IR (Neat): 3350, 1740, 1725  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.99 (3H, s), 2.17 (3H, s), 3.00-3.30 (2H, m), 3.78 (3H, s), 4.75-4.90 (1H, m), 6.00-7.10

(3H, m), 6.37 (2H, br s)

### Preparation 29

The following compounds were obtained according to a  
5 similar manner to that of Preparation 27.

(1) 2-Acetylamino-2-(4-chloro-3-methoxybenzyl)malonic acid  
diethyl ester

mp: 122-123°C

10 IR (KBr): 3247, 2977, 1749, 1643, 1523, 1309, 1205  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.30 (6H, t,  $J=7.1\text{Hz}$ ), 2.03 (3H, s),  
3.64 (2H, s), 3.83 (3H, s), 4.16-4.35 (4H, m), 6.53  
(1H, dd,  $J=2.0$  and  $8.0\text{Hz}$ ), 6.56 (1H, d,  $J=2.0\text{Hz}$ ),  
6.56 (1H, s), 7.23 (1H, d,  $J=8.0\text{Hz}$ )

15 MASS (APCI): 372 ( $\text{M}+\text{H}$ )<sup>+</sup>, 330, 282

(2) 2-Acetylamino-2-(4-fluoro-3-methoxybenzyl)malonic acid  
diethyl ester

mp: 128-131°C

20 IR (KBr): 2981, 1747, 1641, 1520, 1269, 1211  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.30 (6H, t,  $J=7.1\text{Hz}$ ), 2.04 (3H, s),  
3.62 (2H, s), 3.82 (3H, s), 4.27 (4H, q,  $J=7.1\text{Hz}$ ),  
6.48-7.09 (4H, m)

MASS (APCI): 356 ( $\text{M}+\text{H}$ )<sup>+</sup>

25

(3) 2-Acetylamino-2-(3,4-difluorobenzyl)malonic acid diethyl  
ester

IR (Nujol): 3259, 1749, 1645, 1518, 1317, 1277, 1205,  
1051, 1016  $\text{cm}^{-1}$

30 NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 1.16 (6H, t,  $J=7.1\text{Hz}$ ), 1.91 (3H, s),  
3.42 (2H, s), 4.15 (4H, q,  $J=7.1\text{Hz}$ ), 6.76-7.45 (3H,  
m), 8.19 (1H, s)

MASS (APCI): 344 ( $\text{M}+\text{H}$ )<sup>+</sup>, 302

35 (4) 2-Acetylamino-2-[3-methoxy-4-(trifluoromethyl)benzyl]-



malonic acid diethyl ester

mp: 119-120°C

IR (KBr): 3500-3150, 2700-2300, 1637, 1631, 1461, 1348,  
1238, 1172  $\text{cm}^{-1}$

5 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.31 (6H, t,  $J=7.2\text{Hz}$ ), 2.04 (3H, s),  
3.70 (2H, s), 3.84 (3H, s), 4.21-4.36 (4H, m),  
6.57-6.64 (2H, m), 7.44 (1H, d,  $J=8.2\text{Hz}$ )

MASS (APCI): 406 (M+H)<sup>+</sup>, 316

10 (5) 2-Acetylamino-2-(4-fluoro-3-methylbenzyl)malonic acid  
diethyl ester

IR (Neat): 3250, 1740, 1640, 1510, 1460, 1370, 1270,  
1210, 1185  $\text{cm}^{-1}$

15 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.30 (6H, t,  $J=7.1\text{Hz}$ ), 2.03 (3H, s),  
2.22 (3H, s), 3.58 (2H, s), 4.27 (4H, q,  $J=7.1\text{Hz}$ ),  
6.53 (1H, s), 6.70-6.95 (3H, m)

MASS (APCI): 340 (M+H)<sup>+</sup>

### Preparation 30

20 The following compounds were obtained according to a  
similar manner to that of Preparation 28.

(1) N-Acetyl-4-chloro-3-methoxy-DL-phenylalanine

mp: 177-179°C

25 IR (KBr): 3351, 3200-2500, 1735, 1629, 1548  $\text{cm}^{-1}$

MASS (APCI): 272 (M+H)<sup>+</sup>, 230

(2) N-Acetyl-4-fluoro-3-methoxy-DL-phenylalanine

mp: 150-152°C

30 IR (KBr): 3340, 2947, 1718, 1603, 1514, 1259, 1215  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 1.79 (3H, s), 2.74-3.07 (2H, m), 3.81  
(3H, s), 4.41 (1H, m), 6.77 (1H, m), 7.01-7.14 (2H,  
m), 8.17 (1H, d,  $J=8.1\text{Hz}$ ), 12.68 (1H, br)

MASS (APCI): 256 (M+H)<sup>+</sup>

## (3) N-Acetyl-3,4-difluorophenyl-DL-alanine

IR (KBr): 3360, 1710, 1615, 1550, 1530  $\text{cm}^{-1}$ NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 1.78 (3H, s), 2.50-2.88 (2H, m),  
4.35-4.47 (1H, m), 7.07-7.41 (3H, m), 8.19 (1H, d,  
J=8.2Hz)MASS (APCI): 244 (M+H)<sup>+</sup>, 202

## (4) N-Acetyl-3-methoxy-4-trifluoromethyl-DL-phenylalanine

mp: 156-160°C

IR (KBr): 3326, 3200-2300, 1716, 1621, 1552, 1459  $\text{cm}^{-1}$ NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 1.80 (3H, s), 2.85-3.50 (2H, m), 3.87  
(3H, s), 4.23-4.54 (1H, m), 6.94 (1H, d, J=8.0Hz),  
7.13 (1H, s), 7.52 (1H, d, J=8.0Hz), 8.23 (1H, d,  
J=8.1Hz), 12.82 (1H, br s)MASS (APCI): 306 (M+H)<sup>+</sup> (free)

## (5) N-Acetyl-4-fluoro-3-methyl-DL-phenylalanine

IR (Neat): 3350, 1720, 1600, 1540, 1500, 1345  $\text{cm}^{-1}$ NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 1.78 (3H, s), 2.20 (3H, s), 2.71-3.03  
(2H, m), 4.31-4.42 (1H, m), 6.97-8.19 (3H, m),  
12.68 (1H, br s)MASS (APCI): 240 (M+H)<sup>+</sup>

## (6) N-Acetyl-3-fluoro-4-methyl-DL-phenylalanine

IR (Neat): 3300, 1740, 1720, 1600, 1540  $\text{cm}^{-1}$ Preparation 31

The following compounds were obtained according to a  
similar manner to that of Preparation 16.

## (1) N-Acetyl-4-chloro-3-methoxy-D-phenylalanine

mp: 116-117°C

 $[\alpha]_D^{27}$ : -36.6° (C=0.37, MeOH)IR (KBr): 3500-3150, 2700-2300, 1733, 1623  $\text{cm}^{-1}$ MASS (APCI): 272 (M+H)<sup>+</sup>, 230

## (2) N-Acetyl-4-fluoro-3-methoxy-D-phenylalanine

IR (Neat): 3330, 2940, 1728, 1618, 1518, 1275, 1223  $\text{cm}^{-1}$ NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 1.79 (3H, s), 2.70-3.10 (2H, m), 3.81 (3H, s), 4.40 (1H, m), 6.78 (1H, m), 7.01-7.14 (2H, m), 8.18 (1H, d,  $J=8.1\text{Hz}$ ), 12.63 (1H, br)MASS (APCI): 256 (M+H)<sup>+</sup>

## (3) N-Acetyl-3,4-difluoro-D-phenylalanine

IR (KBr): 3395, 1720, 1615, 1545, 1515  $\text{cm}^{-1}$ 

## (4) N-Acetyl-3-methoxy-4-trifluoromethyl-D-phenylalanine

mp: 156-160°C

IR (KBr): 3326, 3200-2300, 1716, 1621, 1552, 1459  $\text{cm}^{-1}$ NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 1.80 (3H, s), 2.85-3.50 (2H, m), 3.87 (3H, s), 4.23-4.54 (1H, m), 6.94 (1H, d,  $J=8.0\text{Hz}$ ), 7.13 (1H, s), 7.52 (1H, d,  $J=8.0\text{Hz}$ ), 8.23 (1H, d,  $J=8.1\text{Hz}$ ), 12.82 (1H, br s)MASS (APCI): 306 (M+H)<sup>+</sup> (free)

## (5) N-Acetyl-4-fluoro-3-methyl-D-phenylalanine

 $[\alpha]_D^{28}$ : -34.60° (C=0.5, MeOH)IR (Nujol): 3400, 1715, 1605, 1530, 1500, 1450, 1240, 1200, 1120  $\text{cm}^{-1}$ NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 1.78 (3H, s), 2.20 (3H, s), 2.71-3.03 (2H, m), 4.31-4.42 (1H, m), 6.97-8.19 (3H, m), 12.68 (1H, br s)MASS (APCI): 240 (M+H)<sup>+</sup>

## (6) N-Acetyl-3-fluoro-4-methyl-D-phenylalanine

 $[\alpha]_D^{29}$ : -46.10° (C=0.5, MeOH)IR (Nujol): 3300, 1705, 1600, 1560  $\text{cm}^{-1}$ Preparation 32

The following compounds were obtained according to a similar manner to that of Preparation 17.

## (1) 4-Chloro-3-methoxy-D-phenylalanine hydrochloride

mp: 218-222°C

 $[\alpha]_D^{27}$ : +3.17° (C=0.52, MeOH)IR (KBr): 3500-3150, 2700-2300, 1739, 1589, 1488  $\text{cm}^{-1}$ 

5 NMR ( $\text{D}_2\text{O}$ ,  $\delta$ ): 3.19 (1H, dd, J=7.5 and 14.5Hz), 3.33 (1H, dd, J=5.7 and 14.5Hz), 3.91 (3H, s), 4.28 (1H, dd, J=5.7 and 7.5Hz), 6.89 (1H, dd, J=1.8 and 8.1Hz), 7.03 (1H, d, J=1.8Hz), 7.42 (1H, d, J=8.1Hz)

MASS (APCI): 230 (M+H)<sup>+</sup>

10

## (2) 4-Fluoro-3-methoxy-D-phenylalanine hydrochloride

mp: 210-220°C (decomp.)

IR (KBr): 1738, 1606, 1520, 1487, 1462, 1417, 1274, 1223, 1209, 1157, 1128  $\text{cm}^{-1}$ 

15 NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 3.13 (2H, m), 3.83 (3H, s), 4.00-4.40 (1H, m), 6.70-6.90 (1H, m), 7.00-7.30 (2H, m)

MASS (APCI): 214 (M+H)<sup>+</sup> (free)

## (3) 3-Methoxy-4-trifluoromethyl-D-phenylalanine hydrochloride

20

mp: 156-160°C

IR (KBr): 3326, 3200-2300, 1716, 1621, 1552, 1459  $\text{cm}^{-1}$ 

25 NMR ( $\text{D}_2\text{O}$ ,  $\delta$ ): 3.19 (1H, dd, J=7.5 and 14.4Hz), 3.33 (1H, dd, J=5.7 and 14.4Hz), 3.86 (3H, s), 4.20-4.26 (1H, m), 6.97 (1H, d, J=8.0Hz), 7.07 (1H, s), 7.58 (1H, d, J=8.0Hz)

MASS (APCI): 264 (M+H)<sup>+</sup> (free)

## (4) 4-Fluoro-3-methyl-D-phenylalanine hydrochloride

30

IR (Nujol): 1735, 1485, 1460, 1375, 1210  $\text{cm}^{-1}$ MASS (APCI): 198 (M+H)<sup>+</sup> (free)

## (5) 3-Fluoro-4-methyl-D-phenylalanine hydrochloride

IR (Nujol): 1730, 1480, 1555, 1250, 1220, 1200  $\text{cm}^{-1}$ 

35

Preparation 33

The following compounds were obtained according to a similar manner to that of Preparation 18.

- 5 (1) 4-Chloro-3-methoxy-D-phenylalanine methyl ester  
hydrochloride

mp: 165-168°C

IR (KBr): 3200-2500, 1745, 1583, 1494  $\text{cm}^{-1}$

10 NMR ( $\text{D}_2\text{O}$ ,  $\delta$ ): 3.22 (1H, dd,  $J=7.5$  and  $14.5\text{Hz}$ ), 3.35 (1H,  
dd,  $J=6.8$  and  $14.5\text{Hz}$ ), 3.85 (3H, s), 3.92 (3H, s),  
4.44 (1H, dd,  $J=6.8$  and  $7.5\text{Hz}$ ), 6.89 (1H, dd,  $J=1.9$   
and  $8.1\text{Hz}$ ), 7.02 (1H, d,  $J=1.9\text{Hz}$ ), 7.44 (1H, d,  
 $J=8.1\text{Hz}$ )

15 MASS (APCI): 244  $(\text{M}+\text{H})^+$

- (2) 4-Fluoro-3-methoxy-D-phenylalanine methyl ester  
hydrochloride

mp: 172-173°C

20 IR (KBr): 1745, 1610, 1581, 1518, 1452, 1398, 1294,  
1273, 1242, 1215, 1163, 1120, 1061, 1028  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 3.13 (2H, d,  $J=6.3\text{Hz}$ ), 3.71 (3H, s),  
3.83 (3H, s), 4.31 (1H, t,  $J=6.3\text{Hz}$ ), 6.70-6.90 (1H,  
m), 7.00-7.30 (2H, m)

25 MASS (APCI): 228  $(\text{M}+\text{H})^+$  (free)

- (3) 3-Methoxy-4-trifluoromethyl-D-phenylalanine methyl ester  
hydrochloride

mp: 158-165°C

IR (KBr): 3326, 3200-2300, 1739, 1617, 1504, 1328  $\text{cm}^{-1}$

30 NMR ( $\text{D}_2\text{O}$ ,  $\delta$ ): 3.29 (1H, dd,  $J=7.5$  and  $14.4\text{Hz}$ ), 3.42 (1H,  
dd,  $J=5.7$  and  $14.4\text{Hz}$ ), 3.85 (3H, s), 3.90 (3H, s),  
4.46-4.55 (1H, m), 7.00 (1H, d,  $J=8.0\text{Hz}$ ), 7.12 (1H,  
s), 7.65 (1H, d,  $J=8.0\text{Hz}$ )

35 MASS (APCI): 277  $(\text{M}+\text{H})^+$  (free)

- (4) 4-Fluoro-3-methyl-D-phenylalanine methyl ester hydrochloride

IR (Nujol): 3200, 1740, 1490, 1450, 1240  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.22 (3H, s), 3.00-3.17 (2H, m), 3.68

5 (3H, s), 4.21-4.28 (1H, m), 7.07-7.18 (3H, m), 8.67 (3H, s)

MASS (APCI): 212  $(\text{M}+\text{H})^+$  (free)

- (5) 3-Fluoro-4-methyl-D-phenylalanine methyl ester hydrochloride

10

IR (Nujol): 1740, 1580, 1510, 1450  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.21 (3H, s), 3.13 (2H, d,  $J=6.0\text{Hz}$ ),  
3.69 (3H, s), 4.29 (1H, t,  $J=6.0\text{Hz}$ ), 6.95-7.28 (3H, m), 8.70 (3H, s)

15 MASS (APCI): 212  $(\text{M}+\text{H})^+$  (free)

- (6) 4-Fluoro-D-phenylalanine methyl ester hydrochloride  
mp: 197.3-197.8°C

IR (KBr): 2989, 2956, 2910, 1745, 1741, 1504, 1490,  
20 1450, 1240, 825  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 3.10 (1H, dd,  $J=7.0$  and  $14.0\text{Hz}$ ), 3.18 (1H, dd,  $J=6.4$  and  $14.0\text{Hz}$ ), 3.67 (3H, s), 4.26 (1H, dd,  $J=6.4$  and  $7.0\text{Hz}$ ), 7.11-7.33 (4H, m), 8.67 (3H, br s)

25 MASS: 198  $(\text{M}+\text{H})^+$  (free)

- (7) 4-Chloro-D-phenylalanine methyl ester hydrochloride  
mp: 210-211°C

IR (KBr): 1743, 1707, 1693, 1645, 1547, 1541, 1514,  
30 1495, 1454, 1240, 1186, 1147, 1126, 1099, 1061, 1024  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 3.00-3.30 (2H, m), 3.68 (3H, s), 4.28 (1H, t,  $J=6.5\text{Hz}$ ), 7.28 (2H, d,  $J=8.4\text{Hz}$ ), 7.40 (2H, d,  $J=8.4\text{Hz}$ )

35 MASS (APCI): 214  $(\text{M}+\text{H})^+$  (free)

- (8) 4-Trifluoromethyl-D-phenylalanine methyl ester  
hydrochloride

mp: 198-199°C

IR (KBr): 3199, 2864, 1741  $\text{cm}^{-1}$

5 NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 3.10-3.30 (2H, m), 3.69 (3H, s), 4.35  
(1H, t,  $J=6.4\text{Hz}$ ), 7.51 (2H, d,  $J=8.1\text{Hz}$ ), 7.71 (2H,  
d,  $J=8.1\text{Hz}$ )

MASS (APCI): 248  $(\text{M}+\text{H})^+$  (free)

10 Preparation 34

The following compounds were obtained according to a  
similar manner to that of Preparation 19.

- (1) (2R)-2-(2-Chloroacetyl-amino)-3-(4-chloro-3-  
15 methoxyphenyl)propionic acid methyl ester

mp: 68-69°C

IR (KBr): 3303, 2954, 1739, 1654, 1538  $\text{cm}^{-1}$

20 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 3.13 (2H, d,  $J=6.0\text{Hz}$ ), 3.75 (3H, s),  
3.88 (3H, s), 4.05 (2H, s), 4.84-4.93 (1H, m), 6.65  
(1H, dd,  $J=1.8$  and  $8.1\text{Hz}$ ), 6.67 (1H, d,  $J=1.8\text{Hz}$ ),  
7.28 (1H, d,  $J=8.1\text{Hz}$ )

MASS (APCI): 320  $(\text{M}+\text{H})^+$ , 288, 260

- (2) (2R)-2-(2-Chloroacetyl-amino)-3-(4-fluoro-3-  
25 methoxyphenyl)propionic acid methyl ester

mp: 86-87°C

IR (KBr): 1726, 1687, 1649, 1614, 1550, 1518, 1454,  
1423, 1419, 1362, 1331, 1273, 1227, 1213, 1186  $\text{cm}^{-1}$

30 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 3.12 (2H, d,  $J=5.8\text{Hz}$ ), 3.75 (3H, s),  
3.87 (3H, s), 4.05 (2H, s), 4.87 (1H, dt,  $J=8.0$  and  
5.8Hz), 6.40-7.20 (3H, m)

MASS (APCI): 304  $(\text{M}+\text{H})^+$

- (3) (2R)-2-(2-Chloroacetyl-amino)-3-(3,4-difluorophenyl)-  
35 propionic acid methyl ester

IR (Neat): 3305, 1470, 1675, 1660, 1515  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.87-3.11 (2H, m), 3.63 (2H, s), 4.03 (3H, s), 4.48-4.57 (1H, m), 7.03-7.41 (3H, m), 8.68 (1H, d,  $J=7.8\text{Hz}$ )

5 MASS (APCI): 292  $(\text{M}+\text{H})^+$

(4) (2R)-2-(2-Chloroacetyl-amino)-3-[3-methoxy-4-(trifluoromethyl)phenyl]propionic acid methyl ester  
mp: 108-109°C

10 IR (KBr): 3315, 2965, 1751, 1648, 1536, 1459, 1421  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 3.10-3.29 (2H, m), 3.76 (3H, s), 3.89 (3H, s), 4.05 (2H, s), 4.87-4.97 (1H, m), 6.73-6.77 (2H, m), 7.00-7.05 (1H, m), 7.75 (1H, d,  $J=8.3\text{Hz}$ )

MASS (APCI): 354  $(\text{M}+\text{H})^+$  312

15

(5) (2R)-2-(2-Chloroacetyl-amino)-3-(4-fluoro-3-methylphenyl)propionic acid methyl ester

IR (Nujol): 3300, 1730, 1540, 1500, 1450  $\text{cm}^{-1}$

20 NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.19 (3H, s), 2.82-3.06 (2H, m), 3.62 (3H, s), 4.06 (2H, s), 4.32-4.53 (1H, m), 6.97-7.13 (3H, m), 8.66 (1H, d,  $J=7.8\text{Hz}$ )

MASS (APCI): 288  $(\text{M}+\text{H})^+$

(6) (2R)-2-(2-Chloroacetyl-amino)-3-(3-fluoro-4-methylphenyl)propionic acid methyl ester

25

IR (Nujol): 3300, 1740, 1660, 1540, 1450, 1360  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.19 (3H, s), 2.85-3.10 (2H, m), 3.63 (3H, s), 4.06 (2H, s), 4.45-4.56 (1H, m), 6.92-7.22 (3H, m), 8.68 (1H, d,  $J=7.8\text{Hz}$ )

30 MASS (APCI): 288  $(\text{M}+\text{H})^+$

(7) (2R)-2-(2-Chloroacetyl-amino)-3-(4-fluorophenyl)-propionic acid methyl ester

35

IR (KBr): 3330, 1735, 1646, 1538, 1509, 1448, 1367, 1226, 1151  $\text{cm}^{-1}$



NMR (CDCl<sub>3</sub>,  $\delta$ ): 3.09 (1H, dd, J=5.8 and 14.0Hz), 3.16  
 (1H, dd, J=5.8 and 14.0Hz), 3.74 (3H, s), 4.03 (2H,  
 s), 4.85 (1H, ddd, J=5.8, 5.8 and 7.9Hz), 6.95-7.12  
 (5H, m)

5

MASS: 274 (M+H)<sup>+</sup>

(8) (2R)-2-(2-Chloroacetyl-amino)-3-(4-chlorophenyl)-  
 propionic acid methyl ester

mp: 87-88°C

10

IR (KBr): 1738, 1662, 1537, 1495, 1491, 1446, 1408,  
 1363, 1265, 1209, 1119, 1090, 1036, 1016 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.90-3.30 (3H, m), 3.75 (3H, s), 4.03  
 (2H, s), 4.70-5.00 (1H, m), 7.05 (2H, d, J=8.0Hz),  
 7.28 (2H, d, J=8.0Hz)

15

MASS (APCI): 290 (M+H)<sup>+</sup>

(9) (2R)-2-(2-Chloroacetyl-amino)-3-[4-(trifluoromethyl)-  
 phenyl]propionic acid methyl ester

mp: 83-84°C

20

IR (KBr): 3294, 1741, 1655, 1547 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 3.12-3.32 (2H, m), 3.76 (3H, s), 4.04  
 (2H, s), 4.86-4.96 (1H, m), 7.25 (2H, d, J=8.1Hz),  
 7.57 (2H, d, J=8.1Hz)

MASS (APCI): 324 (M+H)<sup>+</sup>

25

### Preparation 35

The following compounds were obtained according to a  
 similar manner to that of Preparation 20.

30

(1) (3R)-1-Benzyl-3-(4-chloro-3-methoxybenzyl)piperazine-  
 2,5-dione

mp: 149-150°C

$[\alpha]_D^{27}$ : +6.38° (C=0.47, MeOH)

IR (KBr): 3253, 1658, 1461 cm<sup>-1</sup>

35

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 2.94 (1H, dd, J=4.7 and 13.4Hz), 2.96

(1H, d, J=17.4Hz), 3.14 (1H, dd, J=4.5 and 13.4Hz),  
 3.56 (1H, d, J=17.4Hz), 3.76 (3H, s), 4.21 (1H, d,  
 J=14.6Hz), 4.30-4.35 (1H, m), 4.61 (1H, d,  
 J=14.6Hz), 6.66 (1H, dd, J=1.8 and 8.0Hz), 6.91  
 5 (1H, d, J=1.8Hz), 7.04-7.11 (2H, m), 7.17 (1H, d,  
 J=8.0Hz), 7.26-7.33 (3H, m), 8.38 (1H, br s)

MASS (APCI): 359 (M+H)<sup>+</sup>

10 (2) (3R)-1-Benzyl-3-(4-fluoro-3-methoxybenzyl)piperazine-  
 2,5-dione

mp: 177-179°C

IR (KBr): 3240, 1658, 1516, 1464 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ): 3.00-3.30 (3H, m), 3.61 (1H, d,  
 J=17.7Hz), 3.84 (3H, s), 4.20-4.60 (3H, m), 6.29  
 15 (1H, br s), 6.60-7.50 (8H, m)

MASS (APCI): 343 (M+H)<sup>+</sup>

(3) (3R)-1-Benzyl-3-(3,4-difluorobenzyl)piperazine-2,5-  
 dione

20 IR (KBr): 3313, 3255, 1650, 1515, 1465, 1275 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 2.90-4.70 (7H, m), 6.94-7.32 (8H, m),  
 8.35 (1H, s)

MASS (APCI): 331 (M+H)<sup>+</sup>

25 (4) (3R)-1-Benzyl-3-[3-methoxy-4-(trifluoromethyl)benzyl]-  
 piperazine-2,5-dione

IR (KBr): 3315, 1751, 1648, 1536, 1459, 1421 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 2.89-3.25 (2H, m), 3.19 (1H, d,  
 J=17.5Hz), 3.62 (1H, d, J=17.5Hz), 3.77 (3H, s),  
 30 4.15 (1H, d, J=14.5Hz), 4.30-4.35 (1H, m), 4.68  
 (1H, d, J=14.5Hz), 6.80 (1H, d, J=8.0Hz), 7.00-7.41  
 (7H, m), 8.41 (1H, br s)

MASS (APCI): 393 (M+H)<sup>+</sup>, 351

35 (5) (3R)-1-Benzyl-3-(4-fluoro-3-methylbenzyl)piperazine-2,5-

dione

$[\alpha]_D^{28}$ : -15.60° (C=0.5, DMF)

IR (Nujol): 3250, 3225, 1650, 1430, 1320, 1250  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ): 2.13 (3H, s), 2.81-4.65 (7H, m),

6.83-7.34 (8H, m), 8.33 (1H, s)

MASS (APCI): 327 (M+H)<sup>+</sup>

(6) (3R)-1-Benzyl-3-(3-fluoro-3-methylbenzyl)piperazine-2,5-dione

$[\alpha]_D^{27}$ : -16.90° (C=0.5, DMF)

IR (Nujol): 3250, 1680, 1640, 1460, 1320  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ): 2.17 (3H, s), 2.84-4.69 (7H, m),

6.80-7.34 (8H, m), 8.35 (1H, s)

MASS (APCI): 327 (M+H)<sup>+</sup>

(7) (2R)-2-[N-(Benzylaminoacetyl)amino]-3-(4-fluorophenyl)-propionic acid methyl ester

MASS: 345 (M+H)<sup>+</sup>

(8) (3R)-1-Benzyl-3-(4-fluorobenzyl)piperazine-2,5-dione

mp: 190.1-190.8°C

IR (KBr): 1671, 1656, 1509, 1448, 1334, 1162  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 3.08 (1H, d, J=4.4 and 14.0Hz), 3.19

(1H, d, J=5.9 and 14.0Hz), 3.05 (1H, d, J=17.7Hz),

3.56 (1H, d, J=17.7Hz), 4.33 (1H, m), 4.41 (1H, d,

J=14.3Hz), 4.54 (1H, d, J=14.3Hz), 6.38-7.35 (10H,

m)

MASS: 313 (M+H)<sup>+</sup>

(9) (3R)-1-Benzyl-3-(4-chlorobenzyl)piperazine-2,5-dione

mp: 181-182°C

IR (KBr): 1678, 1649, 1564, 1550, 1516, 1489, 1462,

1433, 1408, 1325, 1273, 1178, 1112, 1090, 1063  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.80-3.30 (3H, m), 3.57 (1H, d,

J=17.6Hz), 4.20-4.40 (2H, m), 4.60 (1H, d,

J=14.3Hz), 6.80-7.50 (9H, m)

MASS (APCI): 329 (M+H)<sup>+</sup>

(10) (3R)-1-Benzyl-3-[4-(trifluoromethyl)benzyl]piperazine-  
2,5-dione

mp: 180-181°C

IR (KBr): 3257, 1678, 1651 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 2.86 (1H, d, J=17.3Hz), 3.00 (1H, dd,  
J=4.8 and 13.5Hz), 3.25 (1H, d, J=4.5 and 13.5Hz),  
3.59 (1H, d, J=17.3Hz), 4.08 (1H, d, J=14.3Hz),  
4.30-4.40 (1H, m), 4.73 (1H, d, J=14.3Hz), 7.05-  
7.32 (7H, m), 7.47 (2H, d, J=8.2Hz)

MASS (APCI): 363 (M+H)<sup>+</sup>

#### 15 Preparation 36

The following compounds were obtained according to a  
similar manner to that of Preparation 21.

(1) (2R)-4-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-  
chloro-3-methoxybenzyl)piperazine

IR (Neat): 1643, 1517 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ): 2.00-5.20 (14H, m), 6.20-8.00 (11H, m)

MASS (APCI): 571 (M+H)<sup>+</sup>

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-  
difluorobenzyl)-4-benzylpiperazine

IR (Neat): 1645, 1515, 1435, 1280, 1180, 1140 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 2.06-4.82 (11H, m), 6.61-8.19 (11H, m)

MASS (APCI): 543 (M+H)<sup>+</sup>

#### 30 Preparation 37

A solution of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)-  
benzoyl]-2-(4-chloro-3-methoxybenzyl)piperazine (2.23 g) and  
1-chloroethyl chloroformate (0.61 ml) in 1,2-dichloroethane  
(10 ml) was stirred under reflux for 15 hours. After

cooling, the reaction mixture was concentrated under reduced pressure. The resulting syrup was dissolved into methanol (10 ml) and the solution was stirred under reflux for 2 hours. After cooling, the reaction mixture was concentrated under reduced pressure and the resulting powder was collected by filtration to give a yellow powder of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-methoxybenzyl)piperazine hydrochloride (2.00 g).

mp: 70-71°C.

MASS (APCI): 481 (M+H)<sup>+</sup>

### Preparation 38

A solution of boron tribromide in dichloromethane (1M solution, 6.0 ml) was added dropwise over 20 minutes to an ice-cooled solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-methoxybenzyl)piperazine hydrochloride (0.98 g) in dichloromethane (5 ml). After being stirred at the same temperature for 2 hours, followed by at room temperature for 12 hours, an additional solution of boron tribromide in dichloromethane (1M solution, 4.0 ml) was added, and the whole was stirred at room temperature for further 4 hours. The resulting mixture was poured into aqueous saturated sodium hydrogen carbonate solution and the whole was stirred for 1 hour. The organic layer was separated, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (20:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)piperazine (0.67 g) as a foam.

IR (Neat): 3400-3000, 1635 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 2.60-4.80 (10H, m), 6.28-7.20 (3H, m),

7.41 (1H, s), 7.75 (1H, s), 8.14 (1H, d, J=8.2Hz),

10.00 (1H, br s)  
MASS (APCI): 467 (M+H)<sup>+</sup>

### Preparation 39

5 The following compounds were obtained according to a similar manner to that of Preparation 38.

(1) (2R)-4-Benzyl-2-(4-chloro-3-hydroxybenzyl)piperazine  
mp: 65-68°C

10 IR (KBr): 2939, 2813, 1444, 1429, 1294, 1236, 1136,  
1047 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 1.60-4.00 (11H, m), 6.60 (1H, dd,  
J=1.6 and 8.0Hz), 6.78 (1H, d, J=1.6Hz), 7.16-7.40  
(6H, m)

15

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-hydroxybenzyl)piperazine

mp: 82-86°C

IR (KBr): 3282, 1637, 1282, 1182, 1136 cm<sup>-1</sup>

20 NMR (CDCl<sub>3</sub>, δ): 2.20-5.20 (10H, m), 6.10-8.10 (6H, m)

MASS (APCI): 451 (M+H)<sup>+</sup>

(3) (3R)-1-Benzyl-3-(3-hydroxy-4-methylbenzyl)piperazine

IR (KBr): 1649, 1516 cm<sup>-1</sup>

25 NMR (CDCl<sub>3</sub>, δ): 1.95-2.20 (2H, m), 2.20 (3H, s), 2.57-  
3.06 (7H, m), 3.51 (1H, d, J=13.1Hz), 3.52 (1H, d,  
J=13.1Hz), 6.60 (1H, d, J=7.4Hz), 6.61 (1H, s),  
7.03 (1H, d, J=7.4Hz), 7.20-7.35 (5H, m)

MASS (APCI): 297 (M+H)<sup>+</sup>

30

### Preparation 40

To a solution of (2R)-2-(4-chloro-3-hydroxybenzyl)-4-benzylpiperazine (3.78 g) and triethylamine (5.71 ml) in dichloromethane was added 4-dimethylaminopyridine (0.29 g)  
35 and tert-butyldimethylsilyl chloride (5.30 g) successively

with ice bath cooling under nitrogen atmosphere. After stirring overnight at room temperature, water (50 ml) was added to the mixture and the organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of dichloromethane and methanol (10:1) as eluent to give (2R)-4-benzyl-2-[4-chloro-3-(tert-butyl dimethylsilyloxy)benzyl]piperazine (4.11 g) as an oil.

IR (Neat): 1600, 1575, 1485, 1420, 1295, 1250, 1170, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.15 (6H, s), 0.96 (9H, s), 1.80 (1H, t,  $J=10.0\text{Hz}$ ), 1.94-2.98 (8H, m), 3.40 (1H, d,  $J=13.0\text{Hz}$ ), 3.48 (1H, d,  $J=13.0\text{Hz}$ ), 6.60-7.34 (8H, m)

MASS (APCI): 431 ( $\text{M}+\text{H}$ )<sup>+</sup>, 397

#### Preparation 41

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.93 g) was added to a mixture of (2R)-4-benzyl-2-[4-chloro-3-(tert-butyl dimethylsilyloxy)benzyl]piperazine (2.90 g) and 3-methoxy-5-(trifluoromethyl)benzoic acid (1.48 g), 1-hydroxybenzotriazole (1.14 g) in dichloromethane (18 ml) at room temperature.. After being stirred for 6 hours at the same temperature, the reaction mixture was poured into a mixed solvent of water (25 ml) and dichloromethane (15 ml). The aqueous layer was adjusted to pH 9 with aqueous sodium hydrogen carbonate solution. The organic layer was separated, washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (52 g) using a mixed solvent of hexane and ethyl acetate (2:1). The fractions containing the objective compound was collected and evaporated under reduced pressure to give a syrup of (2R)-1-[3-methoxy-5-(trifluoromethyl)-benzoyl]-2-[4-chloro-3-(tert-butyl dimethylsilyloxy)benzyl]-4-

benzylpiperazine (3.3 g).

IR (Neat): 2937, 1639, 1603, 1421, 1250, 1173, 1132,  
847  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.13 (6H, s), 1.00 (9H, s), 1.60-5.10  
(11H, m), 3.81 (3H, s), 6.30-8.20 (11H, m)

MASS (APCI): 633 (M)<sup>+</sup>

#### Preparation 42

The following compounds were obtained according to a  
similar manner to that of Preparation 37.

(1) (2R)-1-[3-Methoxy-5-(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)piperazine

mp: 154-157°C

IR (KBr): 3265, 2956, 1624, 1427, 1173, 1128  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.20-4.90 (10H, m), 3.82 (3H, s),  
6.20-7.30 (6H, m), 10.02 (1H, br)

MASS (APCI): 429 (M+H)<sup>+</sup>

(2) (2R)-1-[3-Trifluoromethyl-5-(methylthio)benzoyl]-2-[4-chloro-3-(tert-butyldimethylsilyloxy)benzyl]piperazine

IR (Neat): 1645, 1630, 1420, 1170, 1130  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.18 (6H, s), 1.02 (9H, s), 2.48 (3H, s),  
2.60-5.10 (10H, m), 6.28-8.26 (6H, m)

MASS (APCI): 559 (M+H)<sup>+</sup>

(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[4-fluoro-3-methoxybenzyl]piperazine hydrochloride

mp: 127-134°C

IR (KBr): 2970, 2947, 1645, 1520, 1281, 1184, 1136  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.60-5.20 (12H, m), 6.50-8.30 (6H, m),  
9.60 (2H, br)

MASS (APCI): 465 (M+H)<sup>+</sup> (free)

(4) (2R)-2-(4-Fluoro-3-methoxybenzyl)-1-[3-methoxy-5-



(trifluoromethyl)benzoyl]piperazine hydrochloride

IR (KBr): 1643, 1606, 1518, 1464, 1423, 1377, 1350,  
1321, 1242, 1215, 1173, 1126, 1053, 1038  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.30-5.30 (16H, m), 6.30-7.50 (6H, m)

5 MASS (APCI): 427 (M+H)<sup>+</sup> (free)

(5) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-difluorobenzyl)piperazine hydrochloride

10 IR (KBr): 3435, 2940, 2800, 1645, 1520, 1435, 1365,  
1280, 1185, 1135  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.50-5.17 (9H, m), 6.60-8.45 (6H, m),  
9.63 (2H, br s)

MASS (APCI): 453 (M+H)<sup>+</sup> (free)

15 (6) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[3-methoxy-4-(trifluoromethyl)benzyl]piperazine

IR (Neat): 2952, 1639, 1623, 1461, 1423, 1124  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.60-5.20 (13H, m), 6.40-8.00 (6H, m)

MASS (APCI): 515 (M+H)<sup>+</sup>

20

(7) (2R)-1-[3-Methoxy-5-(trifluoromethyl)benzoyl]-2-[3-methoxy-4-(trifluoromethyl)benzyl]piperazine

IR (Neat): 2950, 1637, 1461, 1423, 1317  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.60-5.20 (15H, m), 6.60-7.60 (6H, m)

25 MASS (APCI): 477 (M+H)<sup>+</sup>

(8) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methylbenzyl)piperazine

IR (Neat): 3350, 1640, 1500, 1430, 1380, 1350, 1275  $\text{cm}^{-1}$

30 NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.00-4.84 (12H, m), 6.69-8.34 (7H, m)

MASS (APCI): 449 (M+H)<sup>+</sup>

(9) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-fluoro-4-methylbenzyl)piperazine

35 IR (Neat): 3300, 1625, 1425, 1275, 1120  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.18 (3H, s), 2.40-4.86 (9H, m),  
6.62-8.20 (6H, m)  
MASS (APCI): 449 (M+H)<sup>+</sup>

5 (10) (2R)-2-(4-Fluorobenzyl)-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine hydrochloride  
mp: 78.8-80.3°C  
IR (KBr): 1513, 1423, 1349, 1172, 1126, 1054  $\text{cm}^{-1}$   
NMR (DMSO- $d_6$ ,  $\delta$ ): 2.50-5.03 (9H, m), 3.82 (3H, s), 6.94-  
10 7.25 (8H, m), 9.56 (1H, br s)  
MASS (APCI): 397 (M+H)<sup>+</sup> (free)

(11) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chlorobenzyl)piperazine hydrochloride  
15 mp: 240-260°C  
IR (Neat): 1658, 1496, 1437, 1387, 1362, 1331, 1282,  
1186, 1132, 1101, 1059, 1018  $\text{cm}^{-1}$   
NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.00-5.30 (9H, m), 6.70-8.50 (7H, m)  
MASS (APCI): 451 (M+H)<sup>+</sup> (free)

20 (12) (2R)-2-(4-Chlorobenzyl)-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine hydrochloride  
IR (KBr): 1643, 1605, 1489, 1464, 1423, 1377, 1350,  
1319, 1271, 1242, 1175, 1128, 1097, 1053  $\text{cm}^{-1}$   
25 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.00-5.40 (13H, m), 6.20-8.20 (7H, m)  
MASS (APCI): 413 (M+H)<sup>+</sup> (free)

(13) (2R)-1-(3,5-Bis(trifluoromethyl)benzoyl)-2-[4-(trifluoromethyl)benzyl]piperazine  
30 NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.30-5.30 (9H, m), 7.26-7.88 (7H, m)  
MASS (APCI): 485 (M+H)<sup>+</sup>

(14) (2R)-1-[3-Methoxy-5-(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine  
35 IR (Neat): 2951, 1632, 1608  $\text{cm}^{-1}$

NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.70-5.10 (9H, m), 3.80 (3H, s),  
6.72-7.87 (7H, m)

MASS (APCI): 447 (M+H)<sup>+</sup>

- 5 (15) (2R)-1-[3-Methoxy-5-(trifluoromethyl)benzoyl]-2-(2-naphthylmethyl)piperazine

$[\alpha]_D^{28.8}$ : -46.15° (C=0.26, MeOH)

IR (Neat): 3740, 1630 cm<sup>-1</sup>

10 NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.5-5.4 (9H, m), 3.55 (3H, s), 6.51 (1H, br s), 6.87 (1H, br s), 7.06 (1H, br s), 6.8-7.9 (7H, m)

MASS (APCI): 429 (M+H)<sup>+</sup>

- 15 (16) (2R)-2-[(1H-Indol-3-yl)methyl]-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine

IR (Neat): 3280, 1620, 1459, 1427 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.60-3.00 (10H, m), 3.74 (3H, s),  
6.70-7.40 (8H, m), 8.25-8.52 (1H, m)

MASS (APCI): 418 (M+H)<sup>+</sup>

20

- (17) (2R)-1-tert-Butoxycarbonyl-2-(3-hydroxy-4-methylbenzyl)piperazine

IR (KBr): 1674 cm<sup>-1</sup>

25 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.37 (9H, s), 2.20 (3H, s), 2.72-3.15 (8H, m), 3.90-3.93 (1H, m), 4.16 (1H, br s), 6.62 (1H, s), 6.68 (1H, d, J=7.6Hz), 7.02 (1H, d, J=7.6Hz)

MASS (APCI): 207 (M+H-Boc)<sup>+</sup>

- 30 (18) (2R)-1-(tert-Butoxycarbonyl)-2-(4-chlorobenzyl)-piperazine

$[\alpha]_D^{27.2}$ : +23.33° (C=0.39, MeOH)

IR (Neat): 3340, 2980, 2870, 2830, 1690, 1410, 1370 cm<sup>-1</sup>

35 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.36 (9H, s), 2.6-3.2 (7H, m), 3.90 (1H, br), 4.18 (1H, br s), 7.15 (2H, d, J=8.4Hz), 7.25

(2H, d, J=8.4Hz)

MASS (APCI): 311 (M+H)<sup>+</sup>

#### Preparation 43

5        The following compounds were obtained according to a similar manner to that of Preparation 41.

(1) (2R)-1-[3-Trifluoromethyl-5-(methylthio)benzoyl]-2-[4-chloro-3-(tert-butyldimethylsilyloxy)benzyl]-4-benzylpiperazine

10        IR (Neat): 1645, 1490, 1420, 1300, 1170, 1130 cm<sup>-1</sup>

      NMR (CDCl<sub>3</sub>, δ): 0.15 (6H, s), 1.00 (9H, s), 1.95-5.02 (11H, m), 2.48 (3H, s), 6.20-8.25 (11H, m)

      MASS (APCI): 649 (M+H)<sup>+</sup>, 615

15        (2) (2R)-4-Benzyl-2-(4-fluoro-3-methoxybenzyl)-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine

      IR (Neat): 1738, 1643, 1628, 1616, 1604, 1516, 1464, 1454, 1417, 1371, 1342, 1273, 1099, 1055 cm<sup>-1</sup>

20        NMR (CDCl<sub>3</sub>, δ): 0.60-5.20 (17H, m), 6.00-7.50 (11H, m)

      MASS (APCI): 517 (M+H)<sup>+</sup>

(3) (2R)-4-Benzyl-1-[3-methoxy-5-(trifluoromethyl)benzoyl]-2-[3-methoxy-4-(trifluoromethyl)benzyl]piperazine

25        IR (Neat): 2811, 1643, 1280, 1180, 1137 cm<sup>-1</sup>

      NMR (CDCl<sub>3</sub>, δ): 2.20-5.20 (17H, m), 6.40-7.50 (11H, m)

      MASS (APCI): 567 (M+H)<sup>+</sup>

30        (4) (2R)-4-Benzyl-2-(4-fluorobenzyl)-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine

      IR (Neat): 1639, 1509, 1460, 1423, 1344, 1128, 1010 cm<sup>-1</sup>

      NMR (CDCl<sub>3</sub>, δ): 2.07 (1H, br), 2.73-4.91 (8H, m), 6.57-7.53 (12H, m)

      MASS: 487 (M+H)<sup>+</sup>

- (5) (2R)-4-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-chlorobenzyl)piperazine

IR (Neat): 1738, 1676, 1647, 1628, 1618, 1498, 1454, 1417, 1387, 1273, 1084, 1068  $\text{cm}^{-1}$

5 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.60-5.20 (11H, m), 6.40-8.70 (12H, m)

MASS (APCI): 541 (M+H)<sup>+</sup>

- (6) (2R)-4-Benzyl-2-(4-chlorobenzyl)-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine

10 IR (Neat): 1707, 1678, 1643, 1630, 1618, 1604, 1516, 1496, 1489, 1477, 1454, 1417, 1392, 1375, 1342, 1317  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.60-5.20 (14H, m), 6.40-8.20 (12H, m)

MASS (APCI): 503 (M+H)<sup>+</sup>

15

- (7) (2R)-4-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine

IR (Neat): 2950, 2800, 1765, 1740, 1640  $\text{cm}^{-1}$

20 NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 1.70-4.30 (11H, m), 7.13 (1H, d, J=7.8Hz), 7.20-7.70 (10H, m), 8.13 (1H, d, J=7.8Hz)

MASS (APCI): 575 (M+H)<sup>+</sup>

- (8) (2R)-4-Benzyl-1-[3-methoxy-5-(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine

25 IR (Neat): 2945, 2812, 1643  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.04-5.10 (11H, m), 3.81 (3H, s), 6.73-7.93 (12H, m)

MASS (APCI): 537 (M+H)<sup>+</sup>

- 30 (9) (2R)-4-Benzyl-1-[3-methoxy-5-(trifluoromethyl)benzoyl]-2-(2-naphthylmethyl)piperazine

$[\alpha]_D^{28.8}$ : -18.34° (C=0.35, MeOH)

IR (Neat): 3740, 1640  $\text{cm}^{-1}$

35 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.9-2.4 (2H, m), 2.6-4.0 (11H, m), 4.4-5.2 (1H, m), 6.4-7.9 (15H, m)

MASS (APCI): 519 (M+H)<sup>+</sup>

(10) (2R)-4-Benzyl-2-[(1H-indol-3-yl)methyl]-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine

IR (Neat): 3280, 1620, 1459 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ): 2.00-5.20 (14H, m), 6.60-7.60 (13H, m),  
7.90 (1H, br s)

MASS (APCI): 508 (M+H)<sup>+</sup>

#### 10 Preparation 44

To a solution of 4-fluoro-3-methoxybenzaldehyde (5 g) in methanol (25 ml) was added dropwise sodium borohydride (368 mg) in 0.1N sodium hydroxide aqueous solution (5 ml) in water bath and the whole was stirred for 1 hour. After the mixture was evaporated under reduced pressure, ethyl acetate and water were added thereto. The organic layer was separated and the water layer was further extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate and concentrated in vacuo to give 4-fluoro-3-methoxybenzyl-alcohol (5.22 g) as an oil.

IR (Neat): 1610, 1516, 1462, 1417, 1315, 1277, 1149,  
1115, 1032 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ): 1.75 (1H, br s), 3.90 (3H, s), 4.64 (2H, s), 6.70-7.20 (3H, m)

#### 25 Preparation 45

The following compounds were obtained according to a similar manner to that of Preparation 26.

30 (1) 4-Fluoro-3-methoxybenzyl chloride

IR (Neat): 1608, 1516, 1462, 1417, 1325, 1284, 1271,  
1219, 1155, 1119, 1032 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ): 3.91 (3H, s), 4.55 (2H, s), 6.70-7.20  
(3H, m)

(2) 3-Methoxy-4-(trifluoromethyl)benzyl chloride

IR (Neat): 1606, 1459, 1272, 1174  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 3.91 (3H, s), 4.73 (2H, s), 6.95 (1H, dd,  $J=0.6$  and 8.0Hz), 7.04 (1H, d,  $J=0.6\text{Hz}$ ), 7.53 (1H, d,  $J=8.0\text{Hz}$ )

#### Preparation 46

The following compound was obtained according to a similar manner to that of Preparation 24.

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methoxybenzyl)piperazine

IR (Neat): 1641, 1633, 1626, 1514, 1475, 1462, 1452, 1446, 1435, 1423, 1417, 1385, 1340, 1336, 1273, 1095, 1063, 1045  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.60-5.40 (12H, m), 6.20-8.60 (6H, m)

MASS (APCI): 465 (M+H)<sup>+</sup>

#### Preparation 47

The following compound was obtained according to a similar manner to that of Preparation 17 followed by a similar manner to that of Preparation 18.

3,4-Difluorophenyl-D-alanine methyl ester hydrochloride

IR (KBr): 3400, 1735, 1610, 1235  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 3.16 (2H, d,  $J=6.6\text{Hz}$ ), 3.70 (3H, s), 4.33 (1H, t,  $J=6.6\text{Hz}$ ), 7.05-7.52 (3H, m), 8.65 (3H, s)

MASS (APCI): 216 (M+H)<sup>+</sup> (free)

#### Preparation 48

28% Sodium methoxide in methanol (50 ml) was added to a solution of 3-fluoro-4-(trifluoromethyl)benzoic acid (20.8 g) in dimethylsulfoxide (200 ml). The mixture was stirred at 90°C for 3.5 hours. After cooling at room temperature, the

resulting mixture was poured into ice-water (1.5 l) and made acidic with diluted hydrochloric acid. After being stirred for 30 minutes, the resulting precipitates were collected by filtration and air-dried to give a colorless powder of

3-methoxy-4-(trifluoromethyl)benzoic acid (22.95 g).

mp: 203-204°C

IR (KBr): 3500-3150, 2700-2300, 1637, 1606, 1459, 1272, 1174  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 3.95 (3H, s), 7.61-7.77 (3H, m), 13.45 (1H, s)

#### Preparation 49

Lithium aluminum hydride (4.53 g) was added by small portions to an ice-cooled solution of 3-methoxy-4-(trifluoromethyl)benzoic acid (23.3 g) in tetrahydrofuran (400 ml) under nitrogen atmosphere, and the mixture was stirred at room temperature for 2 hours. After being cooled with ice, 2N sodium hydroxide (2 ml) was added to the mixture under nitrogen atmosphere. The resulting precipitates were filtered off and washed with tetrahydrofuran, and the filtrate and washings were combined and evaporated under reduced pressure to give a crude oil. The oil was purified by column chromatography on silica gel using a mixture of dichloromethane and methanol (40:1) to give 3-methoxy-4-(trifluoromethyl)benzyl alcohol (20 g) as a colorless oil.

IR (Neat): 3500-3150, 2700-2300, 1637, 1606, 1459, 1272, 1174  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.01 (1H, t,  $J=4.6\text{Hz}$ ), 3.88 (3H, s), 4.72 (2H, d,  $J=4.6\text{Hz}$ ), 6.95 (1H, dd,  $J=0.4$  and 8.0Hz), 7.04 (1H, d,  $J=0.4\text{Hz}$ ) 7.52 (1H, d,  $J=8.0\text{Hz}$ )

#### Preparation 50

A solution of 5-bromo-2-fluorotoluene (6 g) in ethyl ether (10 ml) and a catalytic amount of iodine were added to a suspension of magnesium (960 mg) in ethyl ether (10 ml)



under nitrogen atmosphere and the whole was refluxed for 30 minutes. After cooling, a solution of ethyl orthoformate (5.4 g) in ethyl ether (20 ml) was added to the mixture and the whole was stirred overnight. Sulfuric acid (10%, 20 ml) was added to the mixture and the organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography on silica gel with a mixture of hexane and ethyl acetate (10:1) as eluent to give 4-fluoro-3-methylbenzaldehyde as an oil.

IR (Neat): 1695, 1590, 1495, 1280, 1245, 1110  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.36 (3H, s), 7.10-7.84 (3H, m),  
9.93 (1H, s)

The obtained compound was dissolved in a mixture of methanol and tetrahydrofuran and sodium borohydride was added to the solution. After 1 hour of stirring, the solvent was removed and water was added to the residue. The mixture was made acidic with 10% sulfuric acid, extracted with ethyl acetate, washed with brine, dried over sodium sulfate, and evaporated in vacuo to give 4-fluoro-3-methylbenzylalcohol (1.33 g) as an oil.

IR (Neat): 3300, 1500, 1250  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.28 (3H, s), 4.62 (2H, s),  
6.93-7.26 (3H, m)

#### Preparation 51

Carbon tetrabromide (3.08 g) was added portionwisely to a solution of 4-fluoro-3-methylbenzylalcohol (1.3 g) and triphenylphosphine (2.9 g) in methylene chloride (50 ml) and the mixture was stirred for 1 hour. The solution was washed successively with saturated aqueous sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was triturated with hexane and the resulting precipitate was removed by filtration. The filtrate was evaporated in vacuo and the residue was purified

by column chromatography on silica gel with hexane as eluent to give 4-fluoro-3-methylbenzylbromide (1.28 g) as an oil.

IR (Neat): 1500, 1250, 1200  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.26 (3H, s), 4.45 (2H, s),

5

6.91-7.26 (3H, m)

#### Preparation 52

The following compound was obtained according to a similar manner to that of Preparation 50.

10

3-Fluoro-4-methylbenzylalcohol

IR (Neat): 3350, 1580, 1510, 1420, 1250  $\text{cm}^{-1}$

#### Preparation 53

15

The following compound was obtained by a similar manner to that of Preparation 51 followed by a similar manner to that of Preparation 27.

20

2-Acetylamino-2-(3-fluoro-4-methylbenzyl)malonic acid diethyl ester

IR (Nujol): 3250, 1740, 1630, 1510, 1360  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 1.20 (6H, t,  $J=7.0\text{Hz}$ ), 1.94 (3H, s),

2.19 (3H, s), 3.40 (2H, s), 4.10 (4H, q,  $J=7.0\text{Hz}$ ),

6.67-7.23 (3H, m), 8.13 (1H, s)

25

MASS (APCI): 340 ( $\text{M}+\text{H}$ )<sup>+</sup>

#### Preparation 54

The following compounds were obtained according to a similar manner to that of the first half of Preparation 21.

30

(1) (2R)-4-Benzyl-2-[4-chloro-3-methoxybenzyl]piperazine dihydrochloride

mp: 225-230°C (decomp.)

IR (KBr): 3398, 1460, 1419, 1246, 1030  $\text{cm}^{-1}$

35

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 2.80-4.60 (11H, m), 3.87 (3H, s), 6.86

(1H, d, J=8.1Hz), 7.10 (1H, s), 7.30-7.60 (6H, m),  
9.20-10.80 (3H, br)

MASS (APCI): 331 (M+H)<sup>+</sup> (free)

- 5 (2) (3R)-1-Benzyl-3-(4-fluoro-3-methoxybenzyl)piperazine  
IR (Neat): 1666, 1608, 1516, 1456, 1419, 1321, 1275,  
1217, 1151, 1126, 1034 cm<sup>-1</sup>  
NMR (CDCl<sub>3</sub>, δ): 0.60-3.20 (9H, m), 3.58 (2H, s), 3.86  
(3H, s), 6.50-7.10 (3H, m), 7.10-7.60 (5H, m)  
10 MASS (APCI): 315 (M+H)<sup>+</sup>
- (3) (2R)-4-Benzyl-2-[3-methoxy-4-(trifluoromethyl)benzoyl]-  
piperazine  
IR (Neat): 2938, 2809, 1614, 1583, 1506, 1459, 1421 cm<sup>-1</sup>  
15 NMR (CDCl<sub>3</sub>, δ): 1.84-2.16 (2H, m), 2.50-3.01 (7H, m),  
3.51 (2H, s), 3.88 (3H, s), 6.83-6.85 (2H, m), 7.25-  
7.33 (6H, m), 7.47 (1H, d, J=8.2Hz)  
MASS (APCI): 365 (M+H)<sup>+</sup>
- 20 (4) (2R)-4-Benzyl-2-(4-fluoro-3-methylbenzyl)piperazine  
IR (Neat): 1500, 1450, 1320, 1245, 1205, 1120 cm<sup>-1</sup>  
NMR (DMSO-d<sub>6</sub>, δ): 1.60-3.52 (14H, m), 6.95-7.40 (8H, m)  
MASS (APCI): 299 (M+H)<sup>+</sup>
- 25 (5) (2R)-4-Benzyl-2-(3-fluoro-4-methylbenzyl)piperazine  
IR (Neat): 1575, 1510, 1450, 1320, 1250, 1130, 1110 cm<sup>-1</sup>
- (6) (2R)-4-Benzyl-2-(4-fluorobenzyl)piperazine  
IR (Neat): 2937, 2807, 1508, 1450, 1326, 1135, 827,  
30 742 cm<sup>-1</sup>  
NMR (CDCl<sub>3</sub>, δ): 1.87 (1H, t, J=10.4Hz), 2.14 (1H, dt,  
J=3.8 and 11.0Hz), 2.35-2.94 (7H, m), 3.47 (1H, d,  
J=13.0Hz), 3.53 (1H, d, J=13.0Hz), 6.92-7.32 (9H, m)  
MASS (APCI): 285 (M+H)<sup>+</sup>

(7) (3R)-1-Benzyl-3-(4-chlorobenzyl)piperazine  
IR (Neat): 1670, 1491, 1450, 1406, 1360, 1329, 1136,  
1093, 1036, 1022  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.70-3.80 (11H, m), 7.12 (2H, d,  
J=8.4Hz), 7.20-7.60 (7H, m)  
MASS (APCI): 301 (M+H)<sup>+</sup>

(8) (3R)-1-Benzyl-3-[4-(trifluoromethyl)benzyl]piperazine  
IR (Neat): 2939, 2810, 1676, 1618  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.89 (1H, t, J=10.5Hz), 2.09 (1H, dt,  
J=3.9 and 11.0Hz), 2.55-3.04 (7H, m), 3.49 (1H, d,  
J=13.0Hz), 3.52 (1H, d, J=13.0Hz), 7.25-7.32 (7H,  
m), 7.55 (2H, d, J=8.1Hz)  
MASS (APCI): 335 (M+H)<sup>+</sup>

(9) (3R)-1-Benzyl-3-[4-(trifluoromethyl)benzyl]piperazine  
dihydrochloride  
mp: 212-225°C  
IR (KBr): 3398, 2673, 1458, 1331  $\text{cm}^{-1}$   
NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 3.00-4.50 (11H, m), 7.43-7.76 (9H, m)  
MASS (APCI): 335 (M+H)<sup>+</sup> (free)

#### Preparation 55

The following compounds were obtained according to a  
similar manner to that of the latter half of Preparation 21.

(1) (2R)-4-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-  
fluoro-3-methoxybenzyl)piperazine  
IR (Neat): 1736, 1643, 1616, 1516, 1462, 1454, 1435,  
1425, 1377, 1273, 1103, 1065, 1038  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.60-5.20 (14H, m), 6.20-8.60 (11H, m)  
MASS (APCI): 555 (M+H)<sup>+</sup>

(2) (2R)-4-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-  
methoxy-4-(trifluoromethyl)benzyl]piperazine

IR (Neat): 1643, 1280, 1180, 1137  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.20-5.20 (14H, m), 6.40-8.00 (11H, m)

MASS (APCI): 605 (M+H)<sup>+</sup>

- 5 (3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methylbenzyl)-4-benzylpiperazine

IR (Neat): 1640, 1500, 1430, 1380, 1350, 1275, 1130  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.00-4.83 (14H, m), 6.60-8.21 (11H, m)

MASS (APCI): 539 (M+H)<sup>+</sup>

10

- (4) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-fluoro-3-methylbenzyl)-4-benzylpiperazine

IR (Neat): 1640, 1430, 1280, 1170, 1130  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.00-4.90 (11H, m), 2.16 (3H, s),

15

6.53-8.24 (11H, m)

MASS (APCI): 539 (M+H)<sup>+</sup>

#### Example 9

20 The following compounds were obtained according to a similar manner to that of Example 1 using N,N-diisopropylethylamine instead of potassium carbonate as a base.

- (1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]piperazine dihydrochloride

25

mp: 160-169°C

$[\alpha]_D^{27}$ : +10.0° (C=0.52, MeOH)

IR (KBr): 3500-3150, 2700-2300, 1644, 1423, 1282  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.60-5.00 (25H, m), 6.30-7.25 (3H, m),

30

7.43 (1H, s), 7.79 (1H, s), 8.17-8.22 (1H, m), 10.13

(1H, br s), 11.00-12.00 (2H, m)

MASS (APCI): 624 (M+H)<sup>+</sup> (free)

- (2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methoxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]-

35

ethyl]piperazine dihydrochloride

mp: 180-190°C

$[\alpha]_D^{26.7}$ : +13.90° (C=0.5, MeOH)

IR (KBr): 1676, 1645, 1547, 1516, 1464, 1427, 1392,  
5 1387, 1367, 1321, 1282, 1217, 1184, 1136, 1034 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 2.00-5.40 (28H, m), 6.30-8.30 (6H, m)

MASS (APCI): 622 (M+H)<sup>+</sup> (free)

(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[4-  
10 (trifluoromethyl)benzyl]-4-[2-[(2S)-2-(methoxymethyl)-  
morpholino]ethyl]piperazine dihydrochloride

mp: 146-159°C

$[\alpha]_D^{26.8}$ : +10.67° (C=0.239, MeOH)

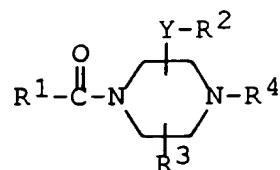
IR (KBr): 3435, 2656, 2598, 2467, 1647, 1429, 1329,  
15 1282, 1180, 1132, 1068 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 2.66-5.32 (27H, m), 7.10-8.30 (7H, m)

MASS (APCI): 642 (M+H)<sup>+</sup> (free)

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula :



wherein

Y is bond or lower alkylene,

R<sup>1</sup> is aryl which may be substituted with suitable  
substituent(s),

R<sup>2</sup> is aryl or indolyl, each of which may be substituted  
with suitable substituent(s),

R<sup>3</sup> is hydrogen or lower alkyl, and

R<sup>4</sup> is (3-pyridyl)methyl;

(3-pyridyl)ethyl;

3-(3-pyridyl)propyl;

3-(3-pyridyl)propenyl;

3-(3-pyridyl)propynyl;

pyrazolylmethyl which may be substituted with  
hydroxy(lower)alkyl;

pyrazolyl(lower)alkyl which is substituted with  
lower alkyl,

(lower)alkoxy(lower)alkylmorpholinyl(lower)alkyl or

(lower)alkoxy(lower)alkylmorpholinylcarbonyl-  
(lower)alkyl;

piperidylmethyl;

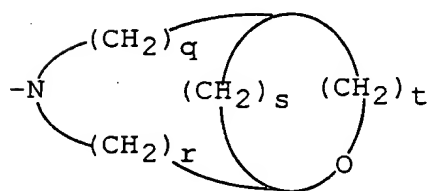
piperidyl(lower)alkyl which is substituted with  
lower alkyl or

(lower)alkoxy(lower)alkyl;

(2,6-dimethylmorpholino)(lower)alkyl;

(3,3-dimethylmorpholino)(lower)alkyl;

(cis-3,5-dimethylmorpholino) (lower) alkyl;  
 ((3S,5S)-3,5-dimethylmorpholino) (lower) alkyl;  
 (2-methoxymethylmorpholino) (lower) alkyl;  
 (3-methoxymethylmorpholino) (lower) alkyl;  
 5 (2-methoxymethyl-5-methylmorpholino) (lower) alkyl;  
 (2-methoxymethyl-5,5-dimethylmorpholino) (lower)-  
 alkyl;  
 (3,5-dimethoxymethylmorpholino) (lower) alkyl;  
 (2,3-dimethoxymethylmorpholino) (lower) alkyl;  
 10 (2-methoxymethylmorpholino) (lower) alkenyl;  
 (5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl) (lower)-  
 alkyl; or  
 lower alkyl which is substituted with a saturated  
 heterocyclic group of the formula :



(wherein

r, s and t are each integer  
 of 1 to 2, and

q is integer of 0 to 2)

which may be substituted with one or two lower  
 alkyl,

and a salt thereof.

2. The compound of claim 1, in which

Y is lower alkylene;

R<sup>1</sup> is phenyl which may be substituted with 1 or 2

substituent(s) selected from the group consisting  
 of lower alkoxy, mono(or di or  
 tri)halo(lower)alkyl, lower alkylthio, lower  
 alkylsulfonyl, di(lower alkyl)aminosulfonyl,  
 pyrrolyl and pyridyl;

R<sup>2</sup> is phenyl which may be substituted with 1 or 2

substituent(s) selected from the group consisting



of lower alkyl, mono(or di or tri)halo(lower)alkyl, halogen, lower alkylenedioxy, lower alkoxy, lower alkoxy(lower)alkoxy(lower)alkoxy, hydroxy, hydroxy(lower)alkyl, cyano, pyrrolidinyl and morpholinyl which may be substituted with lower alkoxy(lower)alkyl or lower alkyl or indolyl;

R<sup>3</sup> is hydrogen; and

R<sup>4</sup> is 3-(3-pyridyl)propyl;

3-(3-pyridyl)propynyl;

(2,6-dimethylmorpholino) (lower)alkyl;

(3,3-dimethylmorpholino) (lower)alkyl;

(cis-3,5-dimethylmorpholino) (lower)alkyl;

((3S,5S)-3,5-dimethylmorpholino) (lower)alkyl;

(2-methoxymethylmorpholino) (lower)alkyl;

(3-methoxymethylmorpholino) (lower)alkyl;

(2-methoxymethyl-5-methylmorpholino) (lower)alkyl;

(2-methoxymethyl-5,5-dimethylmorpholino) (lower)-alkyl;

(3,5-dimethoxymethylmorpholino) (lower)alkyl;

(2,3-dimethoxymethylmorpholino) (lower)alkyl; or

(2-methoxymethylmorpholino) (lower)alkenyl.

3. A compound of claim 2, which is selected from the group consisting of

(1) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[3-hydroxy-4-methylbenzyl]-4-[2-[(3R)-3-(methoxymethyl)morpholino]-ethyl]piperazine,

(2) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine,

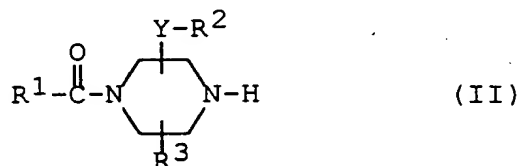
(3) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[2-[(2S,5S)-2-methoxymethyl-5-methylmorpholino]ethyl]piperazine,

(4) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)-2-propynyl]piperazine,

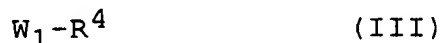
- (5) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine,
- (6) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine,
- (7) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)propyl]piperazine,
- (8) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]piperazine,
- (9) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methoxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]piperazine, and
- (10) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]piperazine,
- or a pharmaceutically acceptable salt thereof.

4. A process for the preparation of the compound of claim 1 or a salt thereof, which comprises,

(1) reacting a compound of the formula (II) :

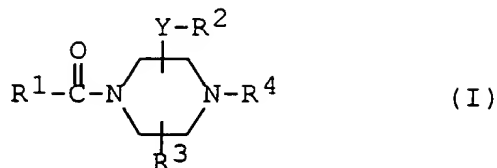


wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and Y are each as defined in claim 1, or a salt thereof, with a compound of the formula (III) :



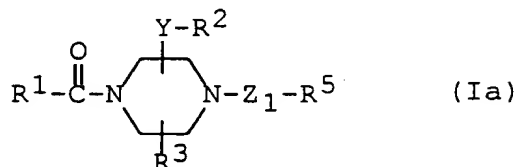
wherein  $\text{R}^4$  is as defined in claim 1 and

$W_1$  is a leaving group,  
or a salt thereof to give a compound of the formula  
(I) :

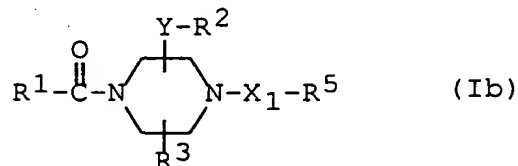


wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and Y are each as defined in  
claim 1,  
or a salt thereof, or

(2) subjecting a compound of the formula (Ia) :



wherein  $R^1$ ,  $R^2$ ,  $R^3$  and Y are each as defined above,  
 $R^5$  is 3-pyridyl, and  
 $Z_1$  is lower alkynylene,  
or a salt thereof to a reduction reaction to give a  
compound of the formula (Ib) :



wherein  $R^1$ ,  $R^2$ ,  $R^3$ , Y and  $R^5$  are each as defined above,  
and  
 $X_1$  is lower alkylene,  
or a salt thereof.

5. A pharmaceutical composition which comprises, as an active ingredient, a compound of calim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.
6. A compound of calim 1 for use as a medicament.
7. A method for treating or preventing Tachykinin-mediated diseases which comprises administering an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof to human being or animals.
8. A compound of claim 1 for use as Tachykinin antagonist.
9. Use of a compound of claim 1 for manufacture of a medicament for treating or preventing Tachykinin-mediated diseases.

DATED this 21st day of October

**Fujisawa Pharmaceutical Co., Ltd**

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Patent Attorneys for the Applicant